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THE TOTAL SYNTHESIS OF (±)-MORPHINE AND (-)-GALANTHAMINE

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THE TOTAL SYNTHESIS OF (±)-MORPHINE AND (-)-GALANTHAMINE

by

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Dedication

Dedicated to my mother, whose countless struggles and unfailing encouragement over the years have made this possible.

Acknowledgements

First and foremost, I would like to thank my parents, Prakash and Manasee Sane and my brother Mihir Sane whose constant support and encouragement through all the ups and downs over the years have made it possible for me to come this far. Dad, I owe my scientific curiosity and acumen to you.

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THE TOTAL SYNTHESIS OF (±)-MORPHINE AND (-)-GALANTHAMINE

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Supervisor: Philip Douglas Magnus

The opiate alkaloid (-)-morphine and the Amaryllidaceae alkaloid (-)-galanthamine are well known for their analgesic and anticholinergic properties, respectively. The chemical feature that connects these two molecules is that they are both biosynthesized from an *ortho-para* phenolic oxidative coupling. Attempts to mimic this aesthetic chemistry in the laboratory for the practical production of these alkaloids have not resulted in good yields of these compounds and there is a lot of scope for improvement. Despite the enormous amount of work devoted to this area, the simple *para*-alkylation of an appropriately substituted phenol derivative to generate a cross conjugated 2, 5-cyclohexadienone has not been reported. This strategy would avoid the low-yielding phenolic oxidation reaction and the product would merely require a double reductive amination of the aromatic aldehyde and the latent aldehyde (in the acetal) to produce narwedine, the synthetic precursor to (-)-galanthamine. On the other hand, the same intermediate can be elaborated to (±)-morphine *via* a Henry reaction, followed by reduction and reductive amination.

Following the aforementioned methodology, we have successfully completed the synthesis of both these alkaloids *via* the common intermediate, a 2, 5-cross-conjugated cyclohexadienone. A demonstration of the use of this methodology towards achieving an enantioselective synthesis of these compounds has also been made. The overall yield of the 8 step procedure for galanthamine proceeds in 65% yield, which is approximately five times the yield of the current manufacturing process for this molecule. The synthesis of (±)-morphine, for the first time, allows access to codeine without having to reduce codeinone and, with an overall yield of 20% for the 14 step process, makes this the shortest synthesis of morphine.

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CHAPTER 1: THE TOTAL SYNTHESIS OF (±)-MORPHINE

1.0 INTRODUCTION

1.1.1 Historical perspective

The unripened seeds of the poppy plant, *Papaver somniferum*, contain a milky white fluid which on exposure to air darkens to a thick black paste which has for centuries been referred to as opium. Opium has been known for its powerfully analgesic and equally euphoric properties since antiquity.[1] The first documented evidence of opium cultivation comes from the Sumerians in Mesopotamia ca. 3400 BC. As trade between the East and West flourished, the knowledge of poppy cultivation, opium production and its usage spread eastward to Persia, India and far-east China and westwards as far as Spain. Opium became stigmatized in Europe ca. 1300 AD during the inquisitions. However, the use of opium for recreational purposes continued in the Islamic and Chinese empires. It was only with the return of Paracelsus from Arabia in 1527, that opium was reintroduced into Western medicine as Paracelsus' laudanum.

By 1729, the use of opium for recreational purposes was so rampant in China that the then emperor of the Qing dynasty introduced prohibition on opium usage. The British East India Company soon discovered that the illicit trade of opium from India to China was a highly profitable venture and illegal trade flourished. Military intervention by the Chinese resulted in the First Opium War and ended with the British conquest of Hong Kong. Following China's second defeat in the Second Opium War, the cultivation of poppy and the production of opium was legalized in China. Within a span of 50 years,

China controlled 85% of the world's production of opium, but, resulted in a staggering 27% of the adult population being addicted.

Following the two World Wars, the global production of opium faced a steady decline with the establishment of democracies in most parts of the world and the advent of communism in other parts, both of which frowned upon the use of opium. This idea was cemented by the United Nations in Article 4 of the Single Convention on Narcotic Drugs and all signatory nations agreed *"to prohibit the import, sale, distribution, export, and use of all narcotic drugs, except for medical and scientific purposes"*.[2]

1.1.2 Medicinal usage

The English physician Thomas Sydenham (1624–1689) improved upon the recipe developed by Paracelsus, and 'laudanum' remained a cornerstone of European medicine well into the nineteenth century. In 1804, the German scientist Sertürner isolated the first active alkaloid extracted from opium and named it 'morphine' (**1**, Figure 1), after Morpheus, the Greek god of dreams.[3] Diacetylmorphine was synthesized from morphine in 1874[4] and later marketed by Bayer and Co. as 'heroin' (**2**). Heroin was found to be approximately 1.5–2 times more potent than morphine on a milligram-for-milligram basis.

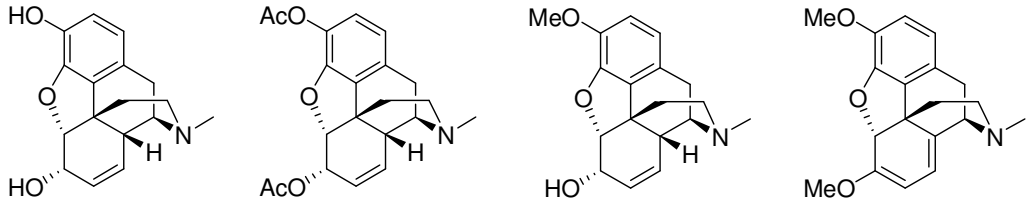


Figure 1.01. Morphine and its congeners.

Morphine (**1**) is the principle constituent of the opium extract along with codeine (**3**), and thebaine (**4**). An average Indian acreage of *Papaver somniferum* yields between 25 and 30 kg of opium per season and, after refining, this will afford approximately 3 kg of morphine (or 300,000 standard medical units).[5] Extraction of opium from *P. somniferum* is a fairly simple process and has remained the same since antiquity. Fifteen days after petal fall, the immature seed capsule of the poppy plant is lanced and the fresh pink opium latex is collected. A day later, the latex, now black in color, is scraped from the capsule and collected. Each capsule is lanced a further three or four times over the following week and more opium is collected. The raw opium is partially dehydrated by sun baking to remove about 90% of its water content; at this point, the black resinous mass, commercially known as Indian opium, contains approximately 10-15% morphine, 3–4% codeine, 0.1–2% thebaine and 0.5–1% papaverine.

While in the past morphine was used to treat everything from insomnia to alcohol abuse, today morphine forms the bedrock of pain management for patients suffering from all moderate to severe pain, including pain associated with HIV/AIDS and cancer. On the World Health Organization's Model List of Essential Medicines, morphine is considered the world's most effective painkiller.

In the year 2000, an estimated 8700 tons of opium and poppy straw concentrate were produced worldwide from over 300,000 hectares of poppy fields. Official figures from the International Narcotics Control Board (INCB) show that just six countries (USA, UK, France, Canada, Germany and Australia) consume about 80% of this global supply, while the developing world, which houses 80% of the world's population, consumes just 5%.[6] This vast disparity is a direct result of the affordability. Naturally the quest for a genuinely practical synthesis of the opiates, one that can compete with the scale of natural supply and price, continues to attract the attention of scientists.

1.1.3 Isolation and Characterization

Investigation into the structure of the alkaloid began soon after its initial isolation. Early studies by Liebig were followed by those of Laurent,[7] who correctly deduced the empirical formula of morphine as $C_{17}H_{19}NO_3$ in 1847. The diacetylation to heroin by Wright proved the presence of two hydroxyl groups.[4] Grimaux demonstrated that a facile monomethylation implied the phenolic nature of one of them.[8] The oxidation of codeine to codeinone established the secondary nature of the other hydroxyl, leading to the assumption that the third oxygen must be an unreactive ether linkage. Hydrogenation established the presence of a double bond and monobromination validated the presence of the aromatic ring. Von Braun degradation (NMe $\rightarrow$ NCN) and Hoffman degradation meant there was a cyclic tertiary amine, and exhaustive Hoffman degradation to produce trimethylamine, ethylene and an aromatic compound, suggested a phenethylamine-type skeleton with a bridged ethylamine linkage. Distillation from zinc dust produced various oxygenated phenanthrenes thus allowing for an assignment of the oxygenation pattern.[9]

After extensive studies with regards to the mysterious ethylamine bridge, Sir Robert Robinson proposed the correct structure of morphine (Figure 1.02) in 1925.[10] It was a remarkable achievement and accounted for every prior and subsequent chemical study of the molecule.[11] In 1955, Hodgkin published the crystal structure of morphine hydroiodide dihydrate thus offering insight into the conformational structure.[12] The absolute configuration of codeine hydrobromide dihydrate was assigned as levorotatory by Kartha.[13]

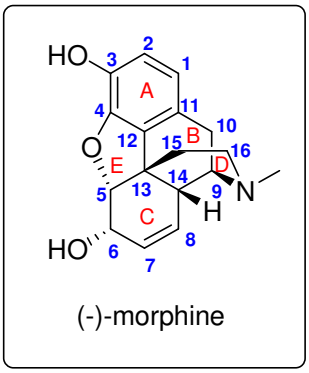


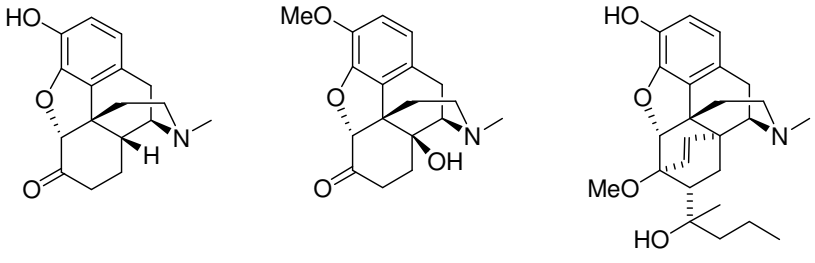
Figure 1.02 Morphine ring system and numbering.

1.1.4 Structure Activity Relationship

Three distinct classes of mammalian opioid receptors μ, δ and κ have been identified as being responsible for the CNS activity of opiates. When coupled with G-proteins they trigger the inhibition of adenylyl cyclase, the enzyme responsible for the production of cyclic adenosylmonophoshate (cAMP) production. The lowering of the cAMP levels affects the potassium (δ and μ receptor agonism) and calcium (κ receptor agonism) ion channels of the cell and, if the opiate use is ceased, leads to a huge surge in the cAMP levels thereby triggering a withdrawal.

Hughes verified the long held belief that morphine mimicked some endogenous analgesics (collectively called endorphins- *end*ogenous m*orphin*oids), compounds which are produced by the body in response to stress or pain.[14] The two enkephalins, met-enkephalin (Tyr-Gly-Gly-Phe-Met) and leu-enkephalin (Tyr-Gly-Gly-Phe-Leu), were characterized by their ability to inhibit the electrically stimulated contraction of guinea pig ileum and mouse vas deferens. The structural similarity to morphine, in that the first residue of each is a tyrosine, is noteworthy.

The structure-activity relationship of the opiates has been well documented.[15] Morphine is selective to the μ-type receptor and thus the analgesia it elicits is accompanied by euphoria, physical dependence and respiratory depression; hence, overdose can be fatal. On the contrary, agonism of the κ-type is analgesic and does not exhibit the side-effects observed in morphine, but instead, is accompanied by strong sedative and dysphoric effects. Most of the morphine produced from opium is converted into codeine by methylation. It is also a precursor for many drugs like hydromorphone (**5**), and oxycodone (**6**), Figure 1.03. Replacement of the *N*-methyl group of morphine with an *N*-phenylethyl group results in a product that is 18 times more powerful than morphine in its opiate agonist potency. Combining this modification with the replacement of the 6-hydroxyl with a 6-methylene produces a compound some 1,443 times more potent than morphine, stronger than the Bentley compounds such as etorphine **7** and as such, is only administered to large animals. The quest for finding analogues that are as potent as the natural opiates, but, which show less of the negative side-effects, continues to draw the attention of researchers in the pain management area.

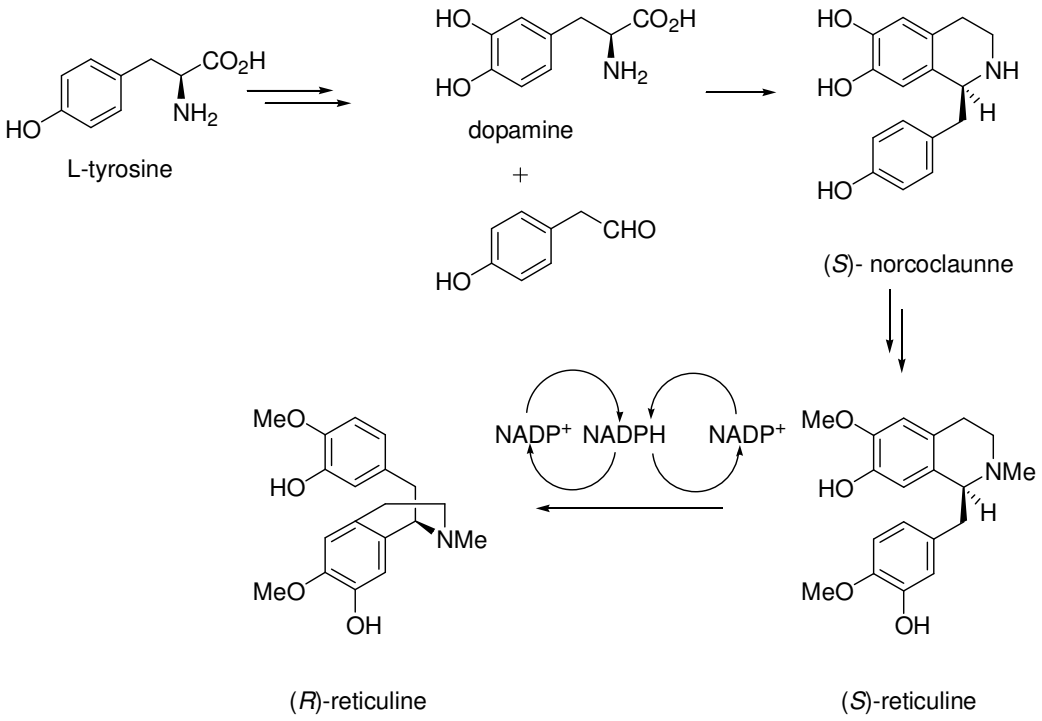


Hydromorphone (**5**) Oxycodone (**6**) Etorphine (**7**)

Figure 1.03. Synthetic opiate drugs.

1.1.5 Biosynthesis

A detailed understanding of the biosynthesis of morphine is now complete.[16] It has been established that the origin of the benzylisoquinoline alkaloid skeleton begins with two molecules of L-tyrosine, Scheme 1.01.



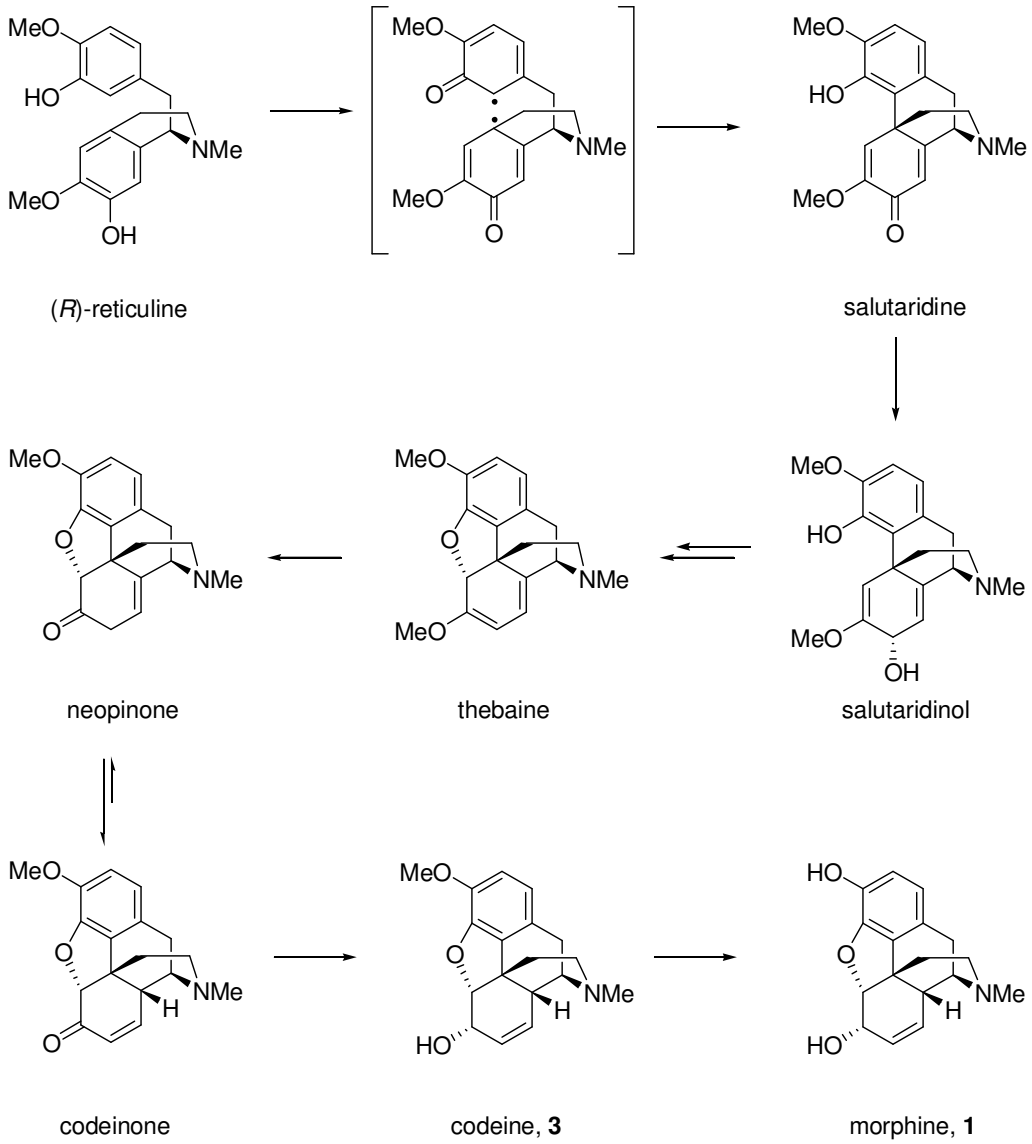
Scheme 1.01 Biosynthesis of (*R*)-reticuline, the phenolic oxidation precursor.

Two equivalents of L-tyrosine are the source of all non-methyl carbon atoms incorporated into morphine, Scheme 1.01. One of the tyrosine molecules is converted into dopamine and the other to *p*-hydroxyphenylacetaldehyde. These are connected by a stereospecific Pictet-Spengler type reaction mediated by (*S*)-norcocalurine synthase to

give (*S*)-norcoclaurine which upon subsequent oxidation and methylation gives (*S*)-reticuline. An inversion of configuration occurs by an NADPH-mediated oxidation-reduction *via* an iminium species to form (*R*)-reticuline. This inversion forms the basis for the exclusive occurrence of (-)-morphine in nature.

The most important step in the biosynthesis of morphine is undoubtedly the diphenolic oxidation using NADPH-dependent cytochrome P450, salutaridine synthase, which forges the link between the two aromatic rings of (*R*)-reticuline and leads to salutaridine, Scheme 1.02. Barton and Cohen originated the idea that this prototypic phenolic coupling forms the basis for many C-C and C-O bonds in a variety of alkaloids, including morphine.[17] Barton demonstrated the conversion of isotopically labeled reticuline to salutaridine by treating it with $K_3Fe(CN)_6$, albeit in a mere 0.02% yield.[18]

Finally, salutaridine is converted to salutaridinol *via* an enzymatic NADPH reduction. Salutaridinol contains the configuration needed for an allylic *syn* displacement, to undergo ring closure and form thebaine. Thebaine is subsequently transformed to neopinone which is then isomerized to codeinone. NADP oxidoreductase in the presence of NADPH reduces codeinone stereospecifically to codeine (**3**). Finally, demethylation of codeine produces morphine (**1**).



Scheme 1.02 .Biosynthetic oxidative phenolic coupling in salutaridine to produce morphine, **1**.

1.1.6 Previous syntheses

The pentacylic ring structure with five contiguous stereocenters, one of which is a quaternary carbon, in a rather limited array of functional groups makes the synthesis of the opiates a challenging task. Thus, Gates' synthesis of morphine in 1952[19] was a landmark publication in this area. To date more than 20 formal and total syntheses have been published, and these have been extensively reviewed in the literature,[20] bearing testimony to the undiminished interest of synthetic chemists in this molecule.

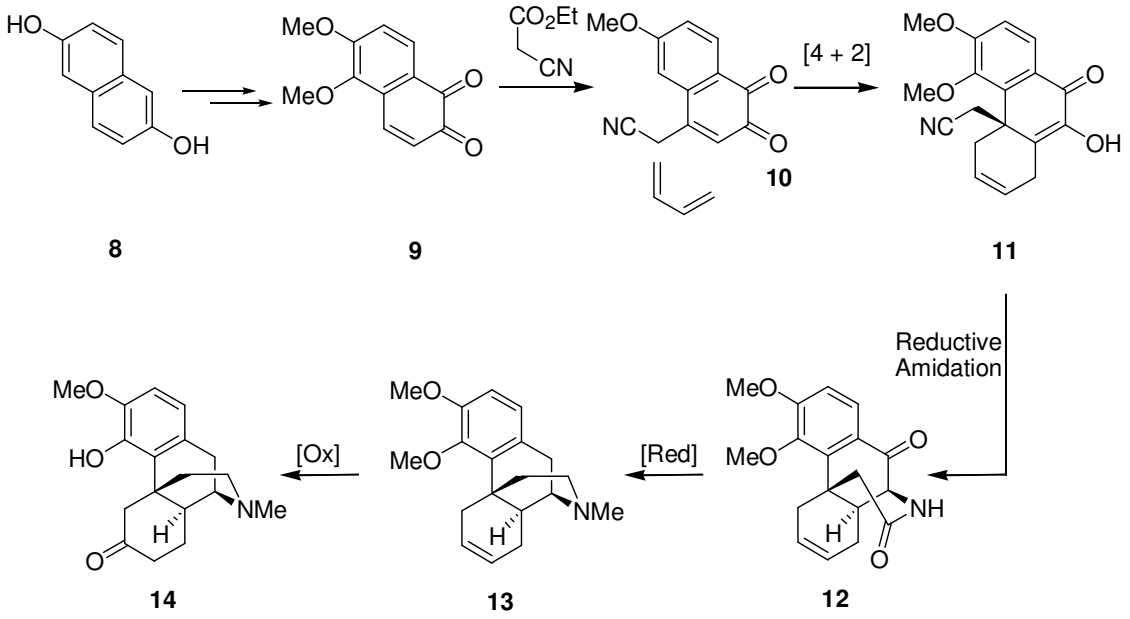
As stated earlier, the bio-mimetic phenolic oxidative coupling of reticuline derivatives have proved to be of limited value in the synthesis of morphine and its congeners. However, formation of the same C12-C13 bond (morphine numbering, unless otherwise stated, Figure 1.02) bond by other methods has led to efficient strategies for opiate syntheses. Unfortunately, except for Rice's synthesis[21] in 1980, no route has shown promise for large-scale manufacturing.

A complete account of all the previous syntheses is beyond the purview of this document and an attempt to classify only the most important syntheses, based on their approach, has been made.

1.1.7 First total synthesis (Gates 1952)

No treatise on the subject of morphine can be complete without outlining the monumental work of Robert Gates who, in 1952, completed the first total synthesis of morphine.[19] This achievement is particularly significant given that the structure was still a subject of debate at the time and the crystallographic evidence came three years after the synthesis was published. The degradation chemistry of morphine usually ended in phenanthrene derivatives, and a majority of the efforts during the time were focused on elaborating the phenanthrene nucleus. Thus, Gates' approach was both unique and bold.

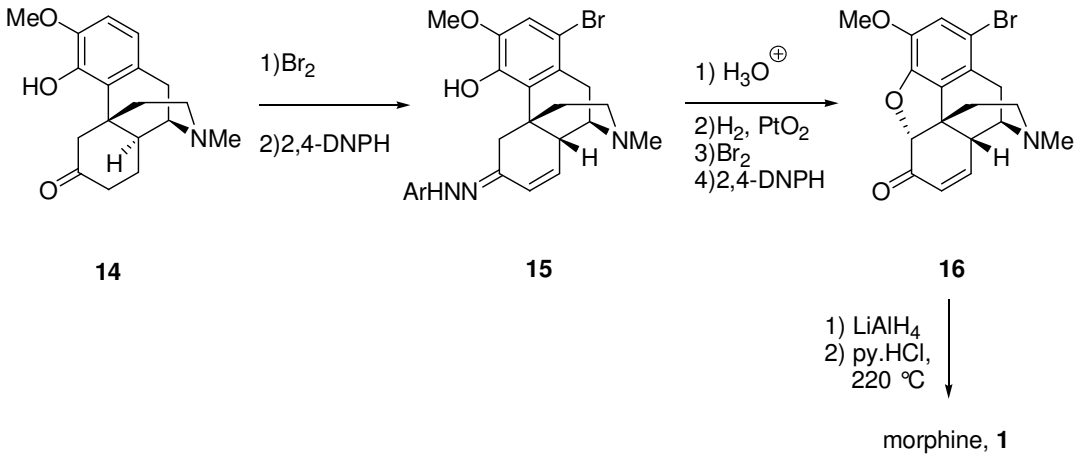
The synthesis commenced with the elaboration of the naphthalene diol **8** to the dione **9**. A Michael-type addition of ethyl cyanoacetate, followed by oxidation, hydrolysis and decarboxylation gave the necessary dienophile for the subsequent Diels-Alder reaction with butadiene to complete the formation of rings A, B and C. This also introduced a two carbon handle at the C13 quaternary center in compound **11**. A unique copper chromite mediated hydrogenation provided the core compound **13**, albeit with the wrong stereochemistry at C14. Oxidation of the alkene **13** produced the β-dihydrothebainone **14**. Most future syntheses invariably intercept Gates' route at this point.



Scheme 1.03. Gates' synthesis of morphine.

The incorrect stereochemistry at C14 required stereochemical correction, Scheme 1.04. The β-dihydrothebainone was treated with bromine followed 2, 4-

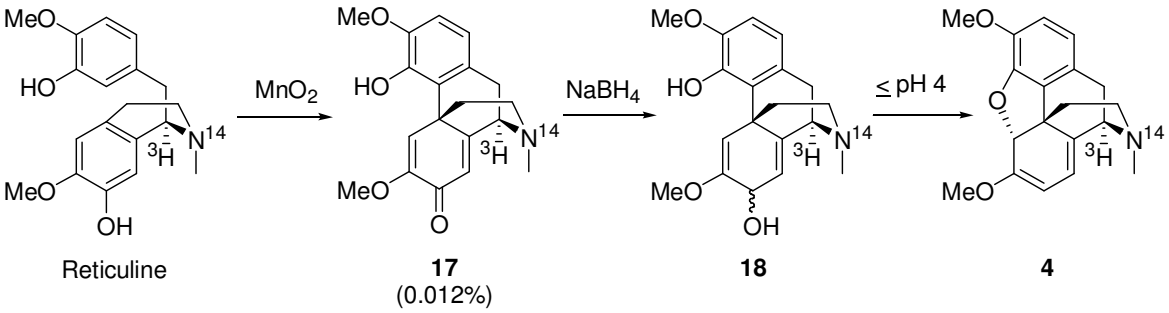
dinitrophenylhydrazine to give the C14 inversion product **15**. This was hydrolyzed to the enone, reduced to the saturated ketone and again treated with bromine. This introduced two bromines, at the C5 and the C7, i.e. both α-positions of ketone **14**. When the ketone **14** was derivatized with 2,4-DNPH, it formed 1-bromocodeinone **16**. Finally, reduction of the codeinone **16** with lithium aluminium hydride produced codeine, which was subjected to a high-temperature demethylation to produce morphine.[22] The overall yield for the 29 step sequence was just 0.001%, but the strategy not only produced the first synthetic sample of morphine, it also succeeded in creating the groundwork for several future syntheses.



Scheme 1.04. Conversion of β-dihydrothebainone (**14**) to morphine.

1.1.8 Phenolic oxidation routes

Barton's previous demonstration of the enzyme mediated phenolic oxidative coupling in labeled reticuline,[23] led to his attempt at achieving this transformation *in vitro*, Scheme1.05. MnO_2 promoted oxidation of reticuline to salutaridine **17** proceeded in a dismal 0.012% yield, and could only be proven with radioisotope dilution experiments. Reduction, followed by S_N2' displacement by the phenolic hydroxyl (**18**) completed the synthesis of radioactive thebaine (**4**).[24]

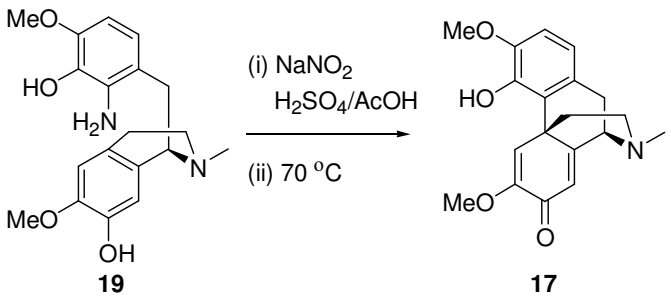


Scheme 1.05. Barton's bio-mimetic synthesis of thebaine.

The non-enzymatic phenolic oxidation process is non-selective and hence forms several products in the process. It was postulated that instead of one electron phenolic oxidations, the use of heterolytic bond formation and scission could potentially alleviate this problem. Schwartz (1975) proposed the use of a hypervalent iodine based oxidant and phenyliodosobis(trifluoroacetate) was identified as the better reagent for this conversion.[25] Unfortunately, the yield did not improve too dramatically and, the method failed to prevent *para-para* coupling. White's synthesis (1983) employed a hypervalent iodine reagent on a substrate bearing a C1-bromine as a blocking group intended to

prevent *para*-coupling.[26] The blocking group idea had gained considerable success in previous strategies directed towards morphine. White's phenolic oxidation step proceeded in a modest 10-21% yield.

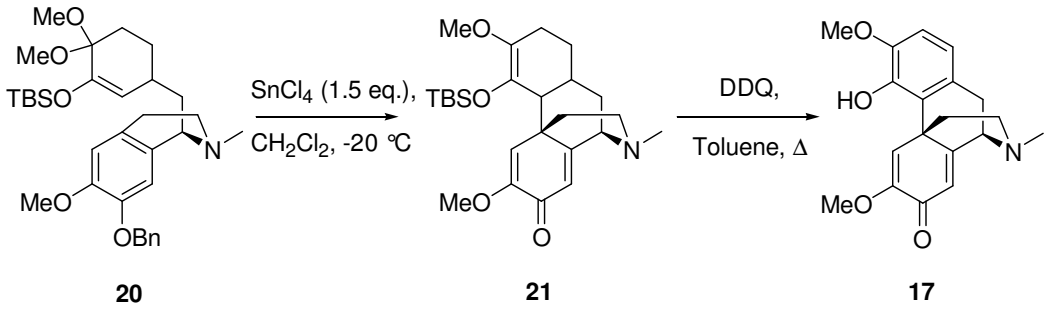
Kametani (1969) employed a Pschorr-type cyclization *via* the diazo derivative of 2-aminobenzyltetrahydroisoquinoline **19**, Scheme 1.06, to achieve a more *ortho*-selective coupling, albeit in a poor 1.1% yield.[27]



19 **17**

Scheme 1.06. Kametani's Pschorr-type cyclization method to form salutaridine (**17**).

Schäfer (1986) employed a non aromatic A-ring moiety (**20**) to achieve the oxidative coupling using $SnCl_4$, followed by aromatization to salutaridine (**17**), Scheme 1.07.[28] Radical mediated coupling was also a feature of Parker's synthesis (1992).[29]

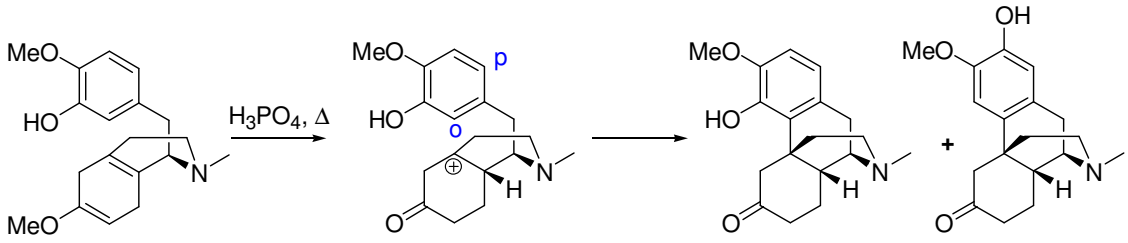


20 **21** **17**

Scheme 1.07 Schäfer's oxidative aryl-alkenyl coupling.

1.1.9 Cationic cyclization

A bioanalogous synthesis was achieved by the combined contributions of several groups (Morrison, Waite and Shavel 1967)[30] and finally adapted to the morphine skeleton by Grewe (1967), using phosphoric acid to effect the key cyclization, Scheme 1.08.[31] The method still suffered from low-regioselectivity and the desired *ortho* coupling proceeded in a poor 3% yield compared to the undesired *para*-coupled product in 37% yield. The acid causes enol ether hydrolysis and trapping of the intermediate cation by the aromatic ring, to produce the *para*-coupled flavinantine and the *ortho*-coupled dihydrothebainone.

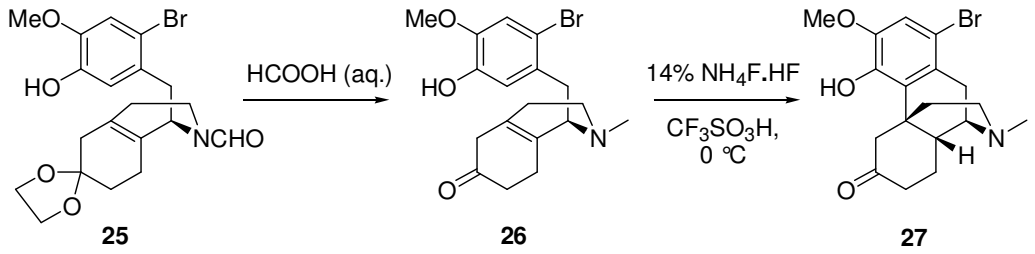


22 **23** (3%) **24** (37%)

Scheme 1.08. Grewe cationic cyclization.

The Grew strategy was improved upon by Beyerman (1979)[32] who introduced a benzyl ether C1-blocking group (to prevent *para*-coupling) to achieve a near-quantitative yield of the coupling product (compound **23** in Scheme 1. 08) and a late-stage hydrogenolysis effected the removal of the blocking group.

This idea was improved upon by Rice (1980),[21] by employing a C1-bromine as the blocking group, Scheme 1.09. The key Grewe-type cyclization on the un-conjugated ketone **25**, with the C1-bromine, proceeded in 60% yield. This method offered a quick assembly of the morphine skeleton in just 8 steps and a remarkable 29% overall yield of compound **27**. This was transformed in 8 additional steps to morphine in an overall yield of 12%. It is therefore considered the most practical synthesis of morphine to date.

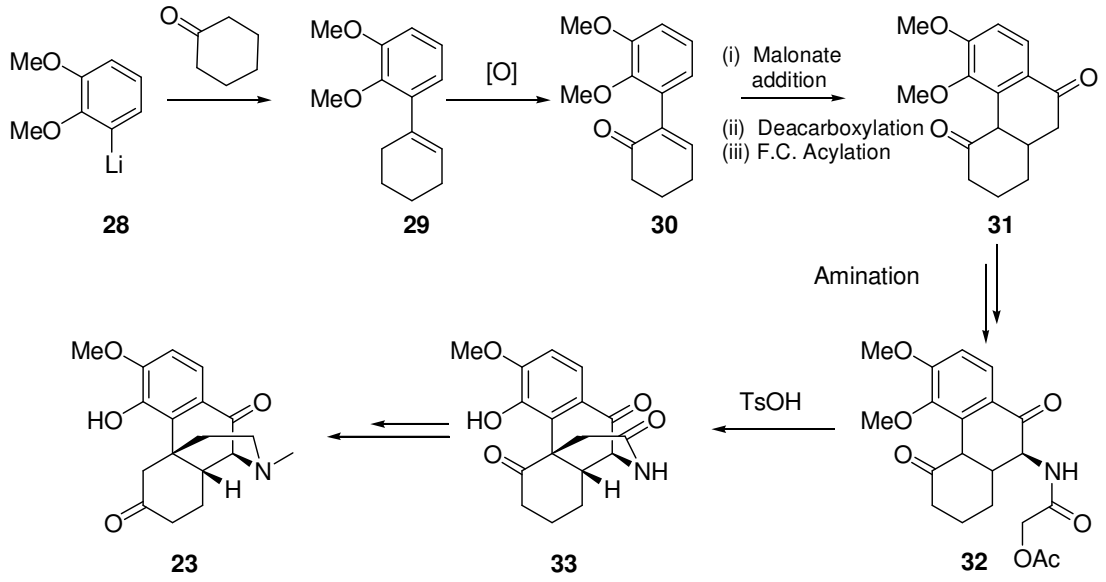


25 **26** **27**

Scheme 1.09. Rice's adaptation of the Grewe strategy.

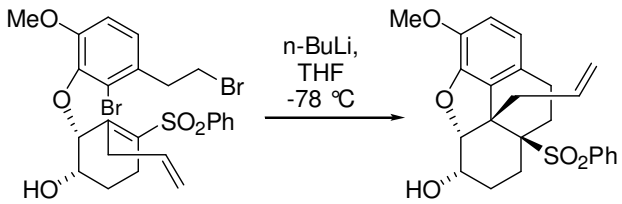
1.1.10 Other C13-C15-bond formations.

As previously stated, a number of early attempts at the assembly of the morphine skeleton were focused on the idea of the elaboration of a phenanthrene core. The crucial step in such strategies is the formation of the C13-C15 bond to generate the quaternary center. Just two years after the first synthesis of morphine was published by Gates, Ginsburg (1954)[33] published the first phenanthrene-based approach. Condensation of *ortho*-lithiated veratrole with cyclohexanone produced the alkene **29** which was transformed to the enone **30**, Scheme 1.10. A Michael addition-decarboxylation-Friedel-Crafts acylation sequence produced the substituted phenanthrene nucleus **31**. Introduction of the acetoxyamide side chain, followed by cleavage of the C4 methyl ether, resulted in a spontaneous formation of the ethylamine bridge. Further elaboration provided the previously synthesized dihydrothebainone **23**.



Scheme 1.10 Ginsberg's approach to the morphine skeleton.

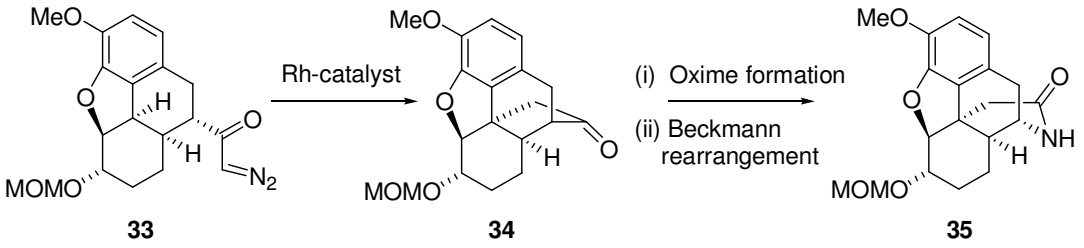
Forty years after publication of the first phenanthrene-based route, which by now had fallen out of popularity, Mulzer (1996)[34] published a synthesis employing a cuprate conjugate addition on the C6 isomer of the enone **30**. Fuchs (1987)[35] employed a tandem conjugate addition-alkylation strategy to combine the two halves of the morphine skeleton and used the previously established stereochemistry at C5 to direct the quaternary center stereochemistry during the conjugate addition, Scheme 1.11.



36 **37**

Scheme 1.11 Fuchs' conjugate addition-alkylation approach

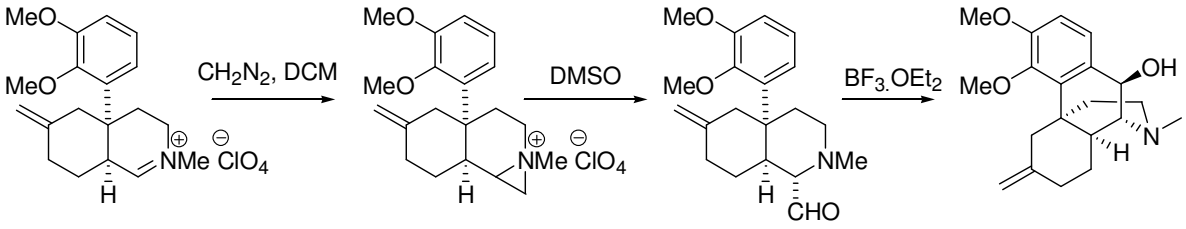
Subsequently, White (1997)[36] revisited the phenanthrene based approach, in his second synthesis, in which the crucial C13-C15 bond was formed *via* a Rh-catalyzed carbenoid C-H insertion reaction using the enantiomerically enriched precursor **33** to provide an enantioselective synthesis of (+)-morphine, Scheme 1.12.



33 **34** **35**

Scheme 1.12 C-H activation approach to the construction of (+)-morphine by White.

Evans' approach (1982) employed an enamine alkylation to synthesize the isoquinoline **38**, Scheme 1.13.[37] Aziridination of the iminium to compound **39** followed by oxidation with DMSO, provided the aldehyde **40**, which upon Lewis acid treatment produced the morphinan **41**. Rapoport's approach (1983) is similar to that of Evans' in many respects, particularly in the initial stages of the synthesis.[38]

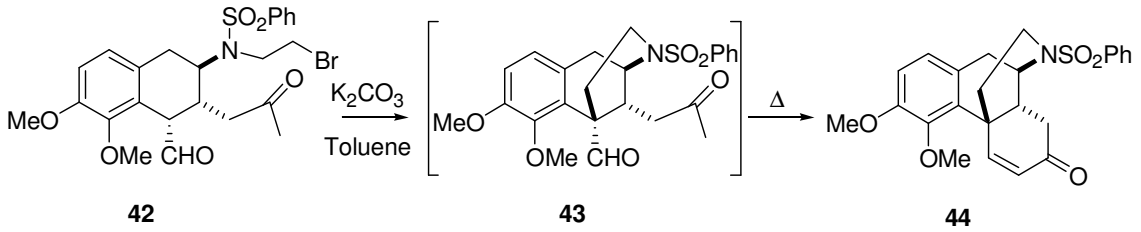


38 **39** **40** **41**

Scheme 1.13 Evans' aziridination approach.

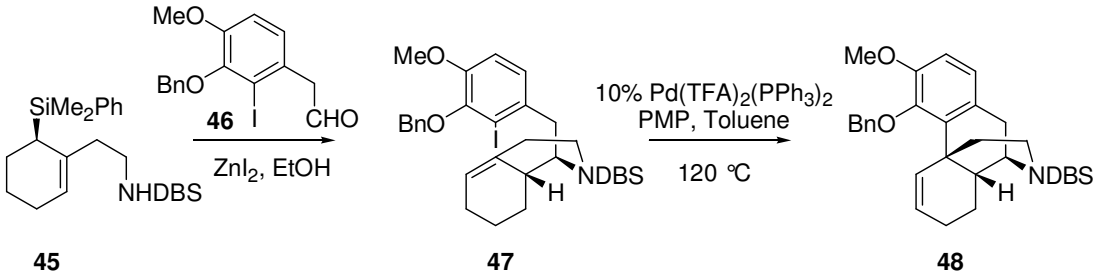
Taber's route (2002) used an intramolecular alkylation-Robinson annulation cascade as the key disconnection in his approach, Scheme 1.14.[39] When the enantiomerically enriched keto-aldehyde **42** was heated under basic conditions, alkylation

(C13-C15 bond formation) produced the bridged compound **43**, which underwent Robinson annulation to give the morphinan **44**.



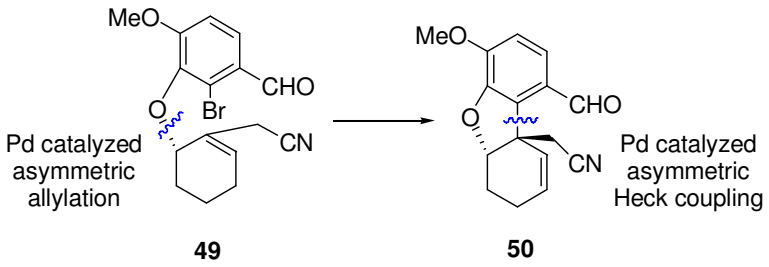
Scheme 1.14 Taber's enolate alkylation approach to form the quaternary center.

The use of palladium mediated cross coupling in the formation of the morphine skeleton was first reported by Overman (1993), Scheme 1.15.[40] Beginning with a stereocontrolled synthesis of allylsilane **45** and subsequent condensation with the aldehyde **46** to produce an intermediate iminium ion, which underwent allylsilane cyclization to afford the isoquinoline **47**. Palladium-mediated coupling resulted in the formation of the C12-C13 bond and produce the morphinan **48**, which was subsequently taken on to complete the first enantioselective synthesis of both (+) and (-)-morphine.



Scheme 1.15 Overman's enantioselective synthesis of morphine.

Trost (2002) utilized two successive palladium catalyzed reactions to form the quaternary center in his synthesis of (-)-morphine, Scheme 1.16.[41]

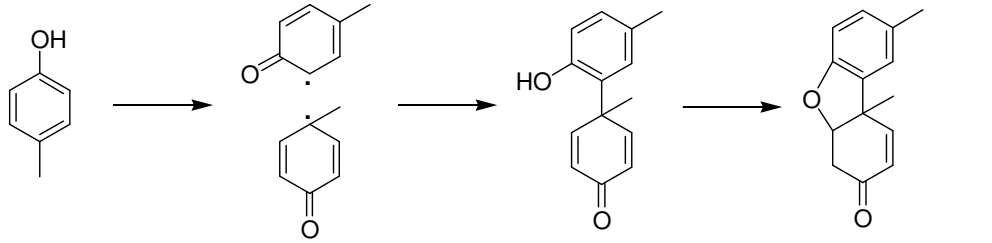


Scheme 1.16 Trost's palladium catalyzed coupling sequence

1.2 STUDIES DIRECTED TOWARDS THE SYNTHESIS OF (±)-MORPHINE

1.2.1 Synthetic strategy

The product of the oxidative coupling of *para*-cresol, known as the Pummerer's ketone, had been postulated as being the core structure for a variety of natural products.[42] Barton argued that the initially proposed structure of the Pummerer's ketone was in fact the product of a dienone-phenol rearrangement, and therefore incorrect. In the course of his studies directed at the synthesis of usnic acid,[43] he demonstrated that the correct structure was in fact compound **52**, Scheme 1.17. A mechanistic rationale for the formation of this product based on the oxidative coupling of *p*-cresol (**51**) was also presented.[44]

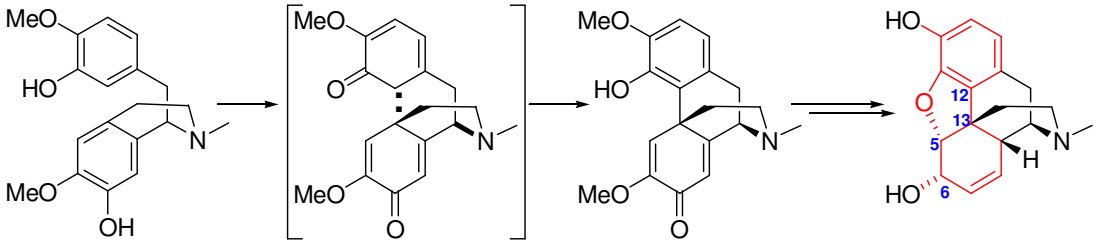


p-cresol, **51**

Pummerer's ketone, **52**

Scheme 1.17 Oxidative coupling of *p*-cresol to produce the Pummerer's ketone (**52**).

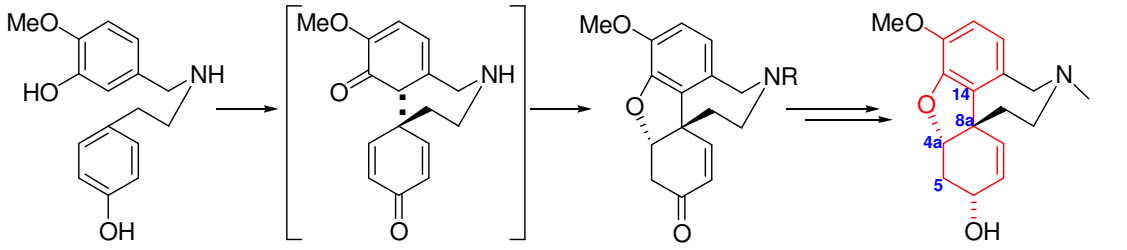
Using this concept, Barton and Cohen demonstrated the *in vitro* oxidation of reticuline to salutaridine by $K_3Fe(CN)_6$ and proposed that this prototypic phenolic oxidative coupling is responsible for the formation of a variety of natural products, including morphine itself, Scheme 1.18.[17]



(*R*)-reticuline, **53** salutaridine, (-)-morphine

Scheme 1.18 Biomimetic synthesis of (-)-morphine (**1**).

Barton and Kirby (1960) extended this idea to the biomimetic synthesis of (±)-galanthamine (**57**) *via* a phenolic oxidative coupling in 4'-*O*-*N*-dimethylnorbelladine, Scheme 1.19.[45] They proposed the symmetrical cross conjugated dienone **55** as the precursor to narwedine (**56**), which in turn was known to be the bio-genetic precursor of galanthamine (**57**).



4'-*O*-methylnorbelladine, **54**

R = H ; *N*-demethylnarwedine, **55**
R = Me; Narwedine, **56**

(-)-galanthamine, **57**

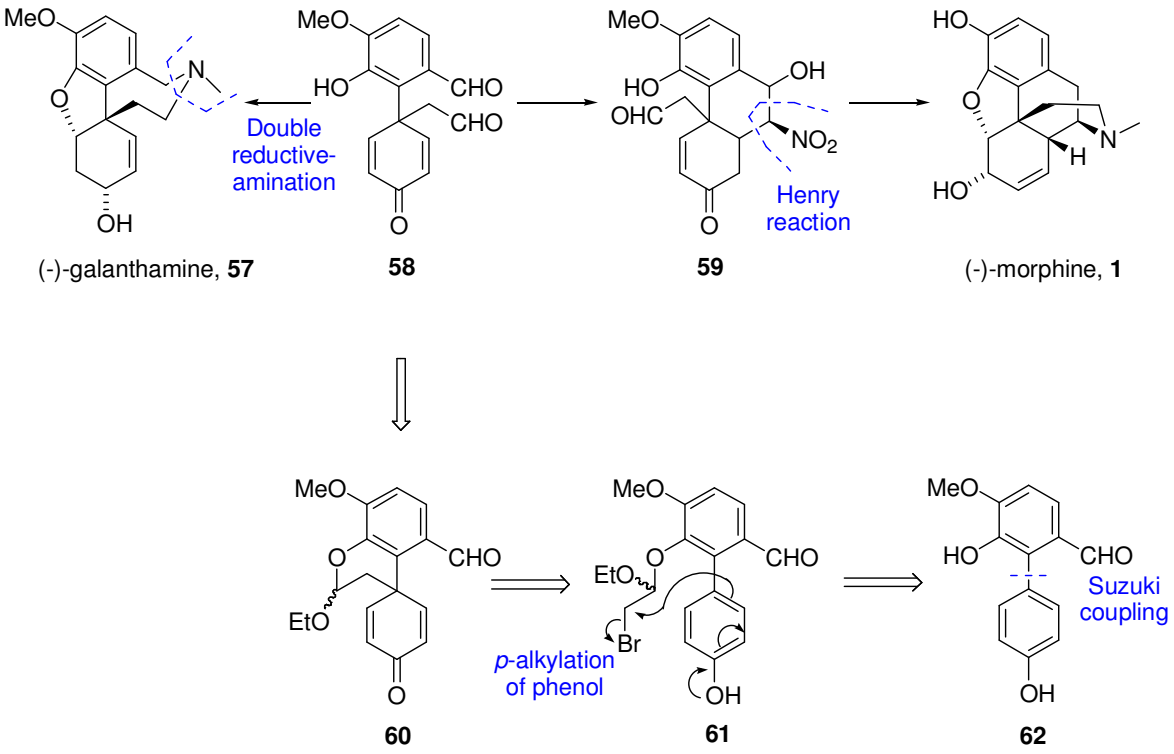
Scheme 1.19 Biomimetic synthesis of (-)-galanthamine (**57**).

Interestingly, in the subsequent full paper (1962) detailing the work, (±)-narwedine **56** was converted to (+)-narwedine with a trace amount of (-)-galanthamine, (**57**). Conversely, (+)-galanthamine was shown to produce (-)-narwedine.[45b] This method was modified and later improved upon by the scientists at Ciba-Geigy, utilizing a catalytic amount of (+)-galanthamine in the dynamic resolution of (±)-narwedine to (-)-narwedine, in very high optical purity and yield, and demonstrated the feasibility on a pilot-scale (kilograms).[46]

The uncanny resemblance of the skeletal arrangement of morphine and galanthamine is quite evident, in that, both resemble the core structure of the Pummerer's ketone. Consequently the strategies used to synthesize these molecules are similar. Most syntheses of galanthamine have attempted to forge the C8a-C14 (galanthamine numbering, Scheme 1.19) bond *via* phenolic oxidations[45a-b,47] or Heck coupling (Fels, Parsons, Guillou/Thal, Trost).[48] The idea that the two natural products can be arrived at using a common intermediate has been utilized by Trost in his divergent synthesis of optically pure morphine and galanthamine, *via* a common intermediate derived from an asymmetric allylic alkylation of phenol derivative.[49]

Based on the biosynthesis of galanthamine, we envisioned that if a cross-conjugated dienone like compound **60** could be synthesized, it could offer the possibility of using the same chemical handles *via* two different transformations to arrive at the two structurally similar natural products, (-)-galanthamine and (-)-morphine, Scheme 1.20. Such a dienone could be doubly reductively aminated (with the free aldehyde and the latent aldehyde in the acetal) to produce racemic narwedine, or be subjected to Henry conditions to form the compound **59** which upon reduction and subsequent reductive amination could provide us with the morphinan skeleton. More importantly, we were

interested in exploring the *para*-alkylation of an appropriately substituted phenol of the type **61** to generate the cross-conjugated dienone **60**.



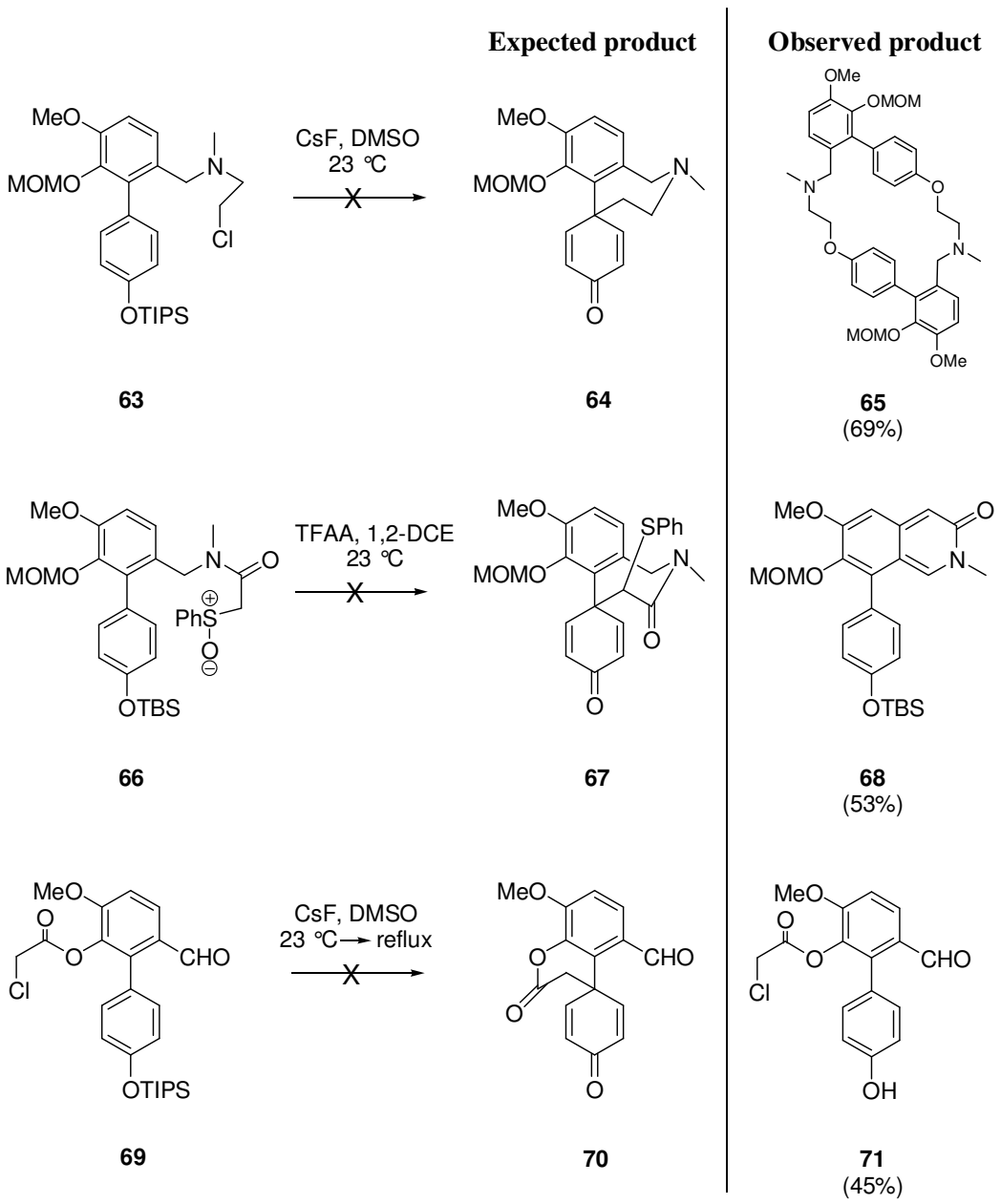
Scheme 1.20 Common dienone intermediate **60**, leading to the two natural products galanthamine and morphine.

The anionic cyclization of phenols is a well established strategy for the synthesis of cross-conjugated dienones and, a wide variety of tethers can be used to create the quaternary centers.[50] Work on utilizing such an approach to the synthesis of galanthamine was initiated in the Magnus group by Dr. Benjamin Fauber, a former graduate student.[51] A summary of his work is represented in Scheme 1.21.

Initial attempts at the arriving at a galanthamine *via* an intramolecular phenolate alkylation of the 1,2-haloethylamine **63** to form the benzoazapine **64**, resulted in only the dimerization product **65** being observed. The dimerization could not be averted, by changing either the solvent concentration or the temperature, and it was reasoned that the necessary orbital overlap could not be achieved in the sp^3 hybridized substitution pattern.

In order to rectify the deficiencies of the previous system, the nature of the electrophile was altered from a sp^3 to sp^2 and in the process also render the carbon more electrophilic. The sulfoxide solvent was expected to induce a Pummerer rearrangement on the halide and render the product **66** more susceptible to attack. However, this approach too was unsuccessful and, the only product observed was the product of electrophilic aromatic substitution-aromatization, compound **68**.

It was then decided that the tether should be placed on the oxygen instead of the benzylic position. This would prevent cyclization onto the aromatic ring, and would force *para*-alkylation. However, the chloroacetate **69** produced only the desilylated phenol **71** upon heating.



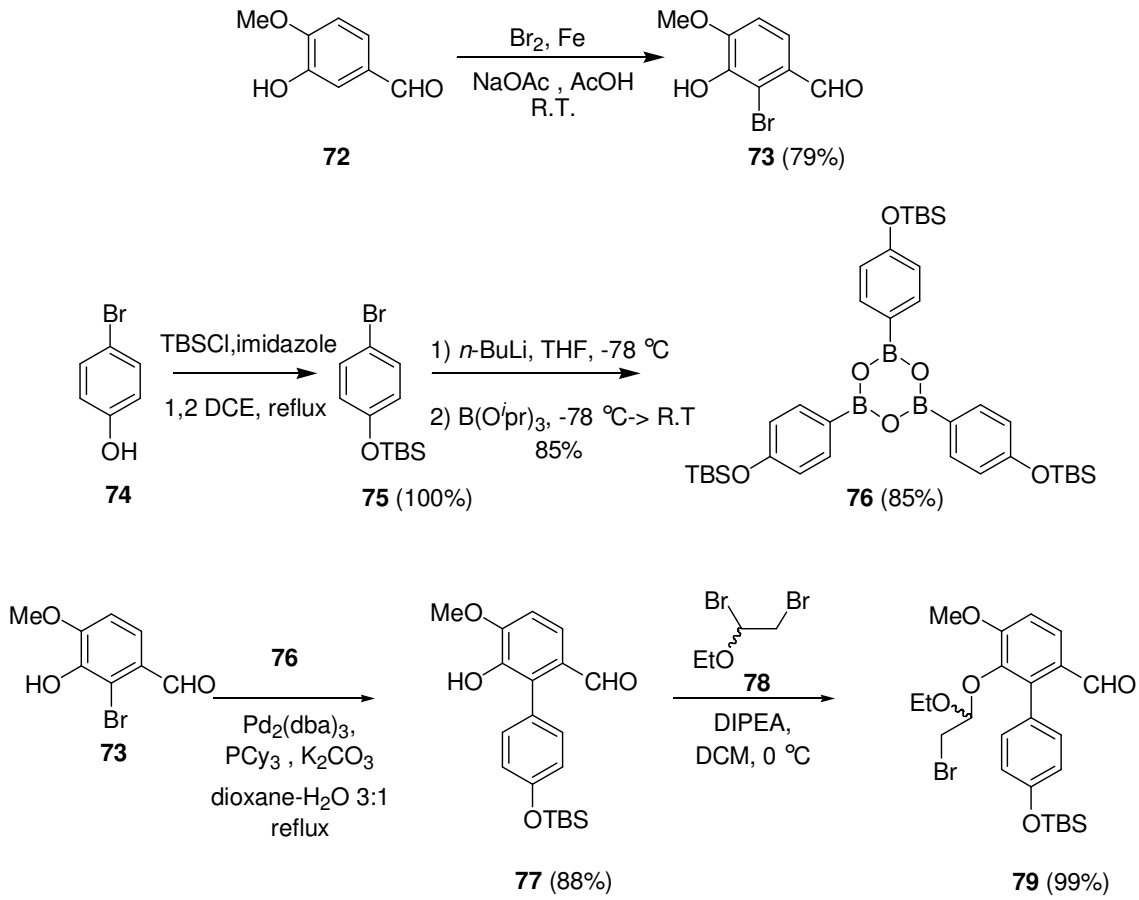
Scheme 1.21. Strategies employed in the synthesis of the cross conjugated dienone.

1.2.2 Synthesis of the dienone intermediate

Although the early strategies employed by Dr. Fauber failed to produce a cross-conjugated dienone, the idea of placing the tether on the phenolic oxygen, was later met with success. A brief discussion of the successful strategy towards the synthesis of a cross-conjugated dienone is now presented.

The first step was the synthesis of the biaryl compound **77** using a Suzuki coupling reaction. The nucleophile in the Suzuki coupling, the bromoaldehyde **73**, can be commerically sourced from Aldrich. However, bearing in mind the multi-gram scale on which this compound would be required to proceed with the investigation, it was found practical to synthesize it by the Friedel-Crafts bromination of isovanillin **72**, commercially available and inexpensive. The boronic acid trimer **76** was prepared in two steps, starting with the protection of the hydroxyl group of commercially available *p*-bromophenol **30** as its TBS-ether and subsequent boronylation with triisopropyl boronate. It was found that the same methodology could also be employed in the synthesis of the TIPS-ether analogue of **76**. However, the TBS-ether trimer **76** could be produced in consistently high yields, in batches of up to 100g, and the resulting product could be conveniently recrystallized from hexanes.

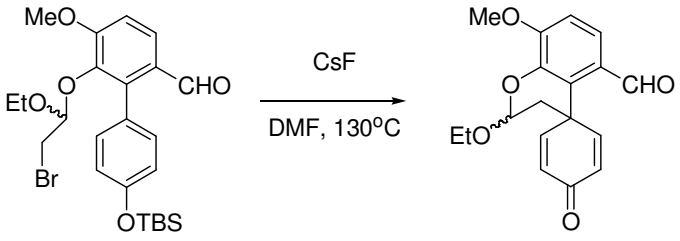
The two fragments **73** and **76** were coupled under Suzuki coupling conditions to form the biaryl compound **77**. It was observed that enhanced yields of the biaryl compound **77** could be obtained when the solvent system was changed from aqueous ethanol (1:3) and aqueous dimethoxyethane (1:3) to aqueous dioxane (1:3). The solvent was degassed, using argon, to remove any dissolved oxygen. BHT was added to the reaction, as an oxygen scavenger, to inhibit oxidative debromination. The biaryl compound **77** was alkylated with 1,2 dibromodiethylether **78** (generated *in situ* by treatment of ethylvinylether with bromine) to produce the bromoacetal compound **79**.



Scheme 1.22 Synthesis of the dienone precursor **79**.

The key intramolecular phenolate alkylation was performed using CsF to desilylate the TBS-protected phenol and generate the phenolate. When the mixture was heated to reflux and maintained at 140 °C, intramolecular phenolate alkylation ensued and complete conversion to the product **60** was obtained, Scheme 1.23. It was important that the reaction be performed under anhydrous conditions; that the CsF and the apparatus be flame-dried under high-vacuum and maintained under an argon atmosphere

before use. Best results were obtained when the DMF was dried over activated 4 Å molecular sieves, for a few days prior to use. When these conditions were strictly adhered to, consistently high yields of 90% and above could be obtained on various scales (0.25-60 g).



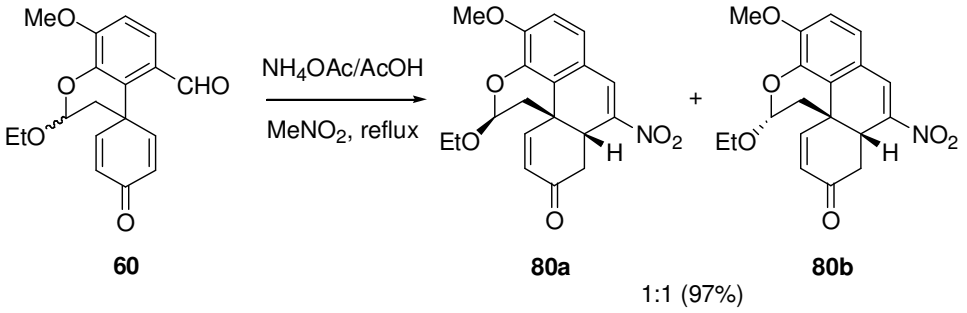
79 **60** (96%)

Scheme 1.23 Intramolecular phenolate alkylation to produce the dienone **60**.

1.2.3 Henry reaction and selective reduction

The course of the present study begins with the conversion of the dienone **60** towards the formation of the morphine skeleton. The first step in this regards required the treatment of the dienone **60** under Henry reaction conditions.[52] When the dienone **60** was treated with nitromethane with a catalytic amount of ammonium acetate in refluxing acetic acid, the nitroalkenes **80a/80b** were obtained as a 1:1 mixture of the two diastereomers in 65% yield after column chromatography. When the same reaction was attempted with a catalytic amount of acetic acid and ammonium acetate in refluxing nitromethane, the crude product was obtained in 97% yield, and pure enough to be carried forward to the next step without chromatography, Scheme 1.24.

It is important to point out here that, only the product of *cis* ring-fusion was obtained. This is presumably due to the fact that the product of *trans* ring-fusion is highly strained in this system. This argument is supported by Spartan energy-minimization calculations which show that the *trans*-isomer is approximately 3 kcal.mol^{-1} higher in energy, as compared to the *cis* isomer

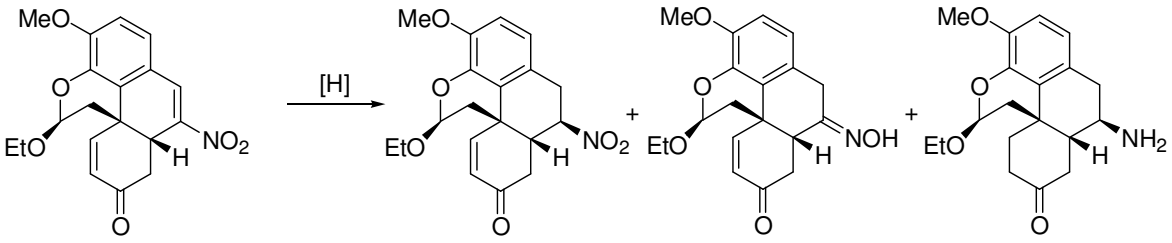


Scheme 1.24 Henry reaction products of the dienone **60**.

With this result in hand, we proceeded to reduce the nitroalkenes **80a/80b** selectively to their corresponding nitroalkanes **81a/81b**, Scheme 1.25. The selective reduction to the nitroalkanes was necessary as it would provide us the opportunity to explore a chiral base catalyzed dynamic resolution to set the absolute stereochemistry at the quaternary center similar to the dynamic resolution of narwedine.[46]

Although nitroalkenes can be reduced to nitroalkanes using a variety of catalysts and reagents,[53] there are no reports of the chemoselective reduction of nitroalkenes in the presence of an enone moiety. An extensive screening of hydrogenation catalysts to selectively reduce nitroalkene **80a** to nitroalkane **81a** was performed. Pd/C, Pd-$BaSO_4$, Pd-$CaCO_3$, Pd-Black,[54] PtO_2, Raney Nickel, Zn/AcOH, Al-amalgam and Wilkinson's

catalyst proved ineffective in that, they either returned unreacted starting material or, produced the oxime (**82a**) which eventually went to the fully reduced product **83a**, Scheme 1.25.

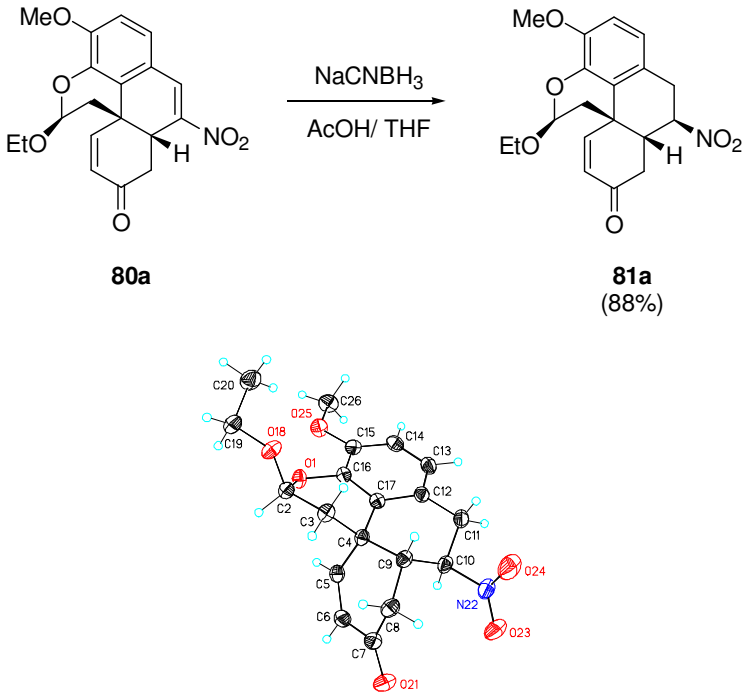


80a **81a** **82a** **83a**

Scheme 1.25 Products of catalytic reduction.

Hydride based reducing agents like $NaBH_4$, $Na(OAc)_3BH$, $LiBH_4$ predominantly reduced the enone moiety in a 1,2 manner, accompanied by the desired conjugate reduction of the nitroalkane.[55] When $NaBH_4$ in 10:1 THF-MeOH was used,[56] an 80% yield of the desired nitroalkane (**81a**) was obtained. *In situ* formation of sodium trimethoxyborohydride from $NaBH_4$ in MeOH has been implicated as the reactive species under these reduction conditions.[57] The use of commercially available sodium trimethoxyborohydride offered improved yields in this chemoselective conversion. When sodium cyanoborohydride was employed as the reducing agent only traces of the product were seen after 4h. However, with the addition of phosphate buffer (pH = 4.5), complete conversion was obtained after 4h. Sodium cyanoborohydride is known to work best at

pH~ 3-5 for this reduction.[58] Subsequently, it was found to be more practical to replace the phosphate buffer with acetic acid. The optimized reaction conditions are depicted in Scheme 1.26.



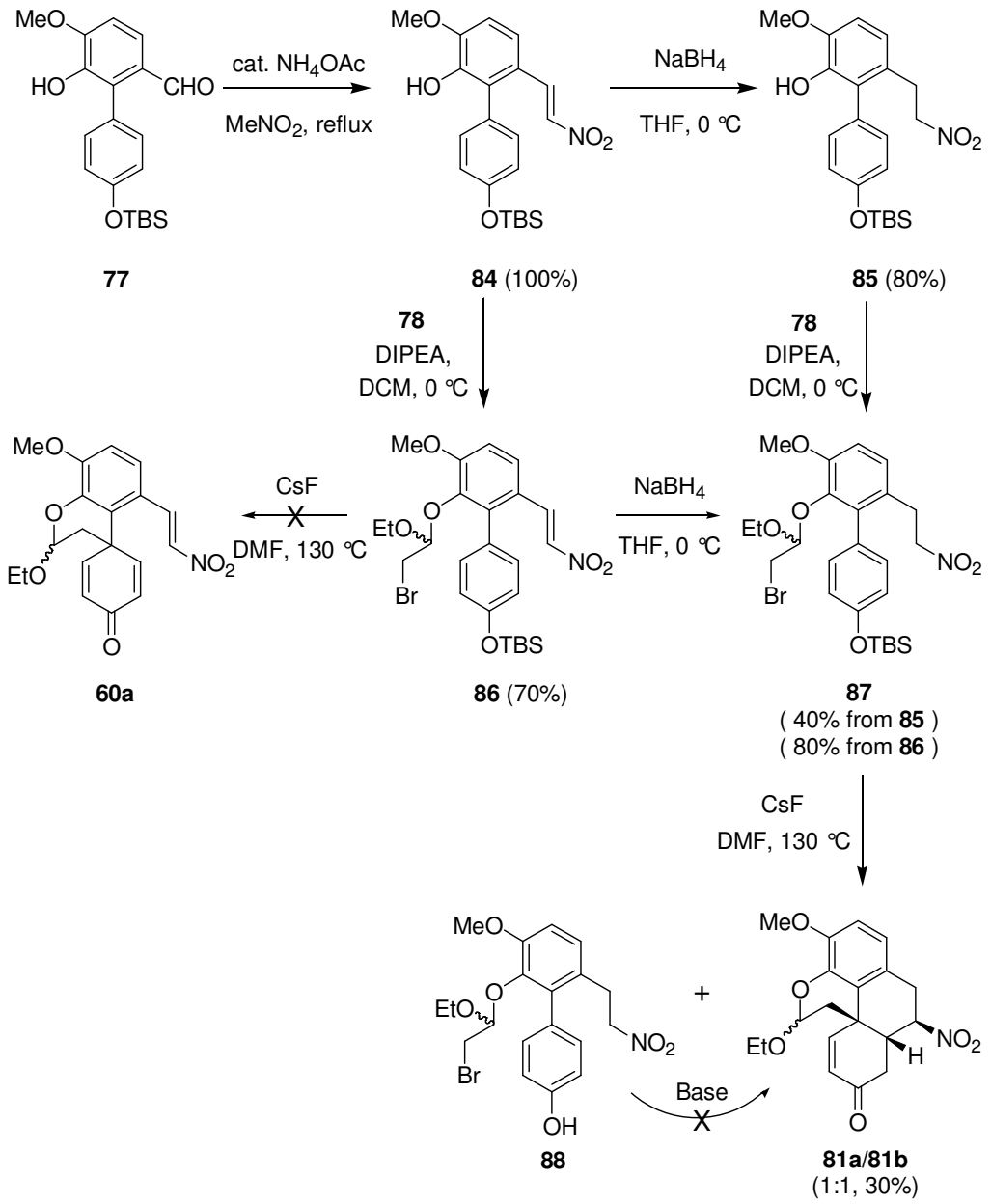
80a **81a** (88%)

Scheme 1.26. Selective reduction to the nitroalkane **81a** and ORTEP illustration of **81a.**

X-ray crystal structure of nitroalkane **81a** revealed that the nitro group was equatorial, and hence, on the same face as the tethered acetal. This was of critical importance, given that the impending reductive amination in the synthetic strategy between the tethered acetal and the amine (which would come from the reduction of the nitro group) could only be possible if the two groups were on the same face, Scheme 1.20.

This seemingly fortuitous result can be easily explained if one considers that the initial product of conjugate reduction is a nitronate anion, which is preferentially protonated from the axial face. Alternatively if one were to invoke a thermodynamic argument, the acetic acid which can engage in reversible protonation-deprotonation, will eventually equilibrate the large nitro group to the less sterically encumbered equatorial position.

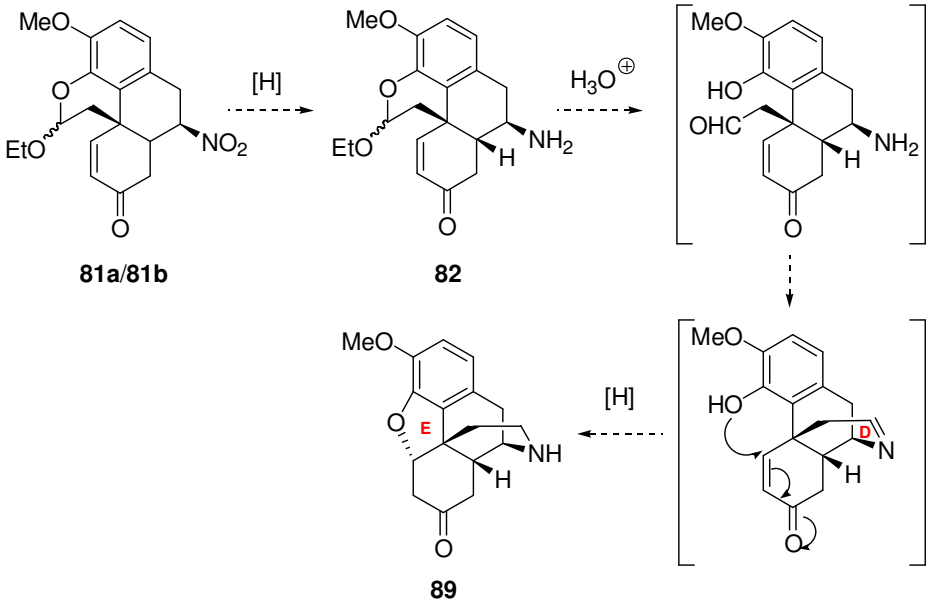
Interestingly, the nitroalkanes **81a/81b** can also be synthesized by an alternative methodology from the biaryl compound **77**, Scheme 1.27. The biaryl compound can be treated under Henry reaction conditions to produce the β-arylnitroalkene **84** which upon reduction with sodium borohydride, gave the β-arylnitroalkane **85**. This upon alkylation with 1,2-dibromoethylether **78**, produced the compound **87**. Compound **87** can also be obtained by changing the sequence of the two preceding reactions *via* compound **86**. When compound **86** was treated under the phenolate alkylation conditions previously used in the synthesis of the dienone **60**, the reaction failed to produce the expected corresponding cross-conjugated dienone with the pendant nitroalkene compound **60a**. Attempts at performing an intramolecular phenolate alkylation on compound **87** to give the nitroalkanes **81a/81b** were successful, but, gave us poor yields of the desired compound. The reaction predominantly produced the protodesilylation product **88**. Attempts at converting compound **88** to compound **81/81b** by treatment with KO*t*Bu failed to achieve the transformation in a variety of solvents even at elevated temperatures under sealed tube conditions. Despite its advantages of high yields and ease of purification by crystallization of all the intermediates, this strategy had to be abandoned due to low yields of the nitroalkane **81a/81b** in the key phenolate alkylation step.



Scheme 1.27 Alternative synthesis of the nitroalkanes 81a/81b.

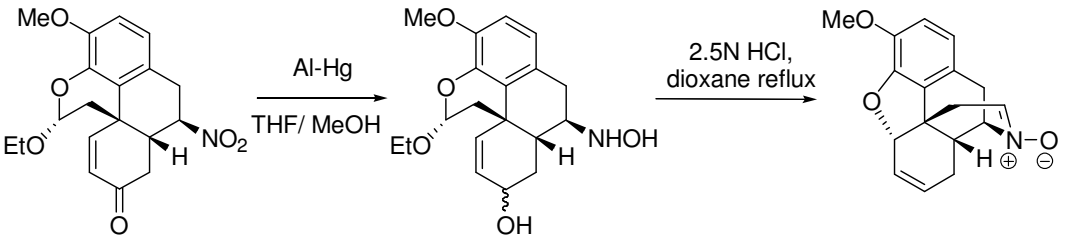
1.2.4 Construction of pentacyclic core and completion of formal synthesis

The next step in the synthesis required the selective reduction of the nitro group of **81a/81b** to the primary amine **82**, Scheme 1.28. Catalytic hydrogenation over Pd/C returned starting material. Hydrogenation with Raney Nickel as catalyst produced the amine **82** in about 45% yield. Thus, similar to the selectivity problem encountered in the conjugate reduction of the nitroalkenes **80a/80b**, the reduction of the nitro group to the amine, while still keeping the enone intact, was unsuccessful. The key idea in the strategy to morphine envisioned the formation of the ethylamine bridge (D-ring) *via* a sequential hydrolysis of the acetal in compound **82** followed by reductive amination with the primary amine. Subsequent conjugate addition of the free phenol would then effect the E-ring closure to form the morphinan **89**. Hence, the reduction of the nitro group to the amine, with retention of the enone, was deemed critical at this stage of the synthesis.



Scheme 1.28. Proposed hydrolysis-reductive amination strategy.

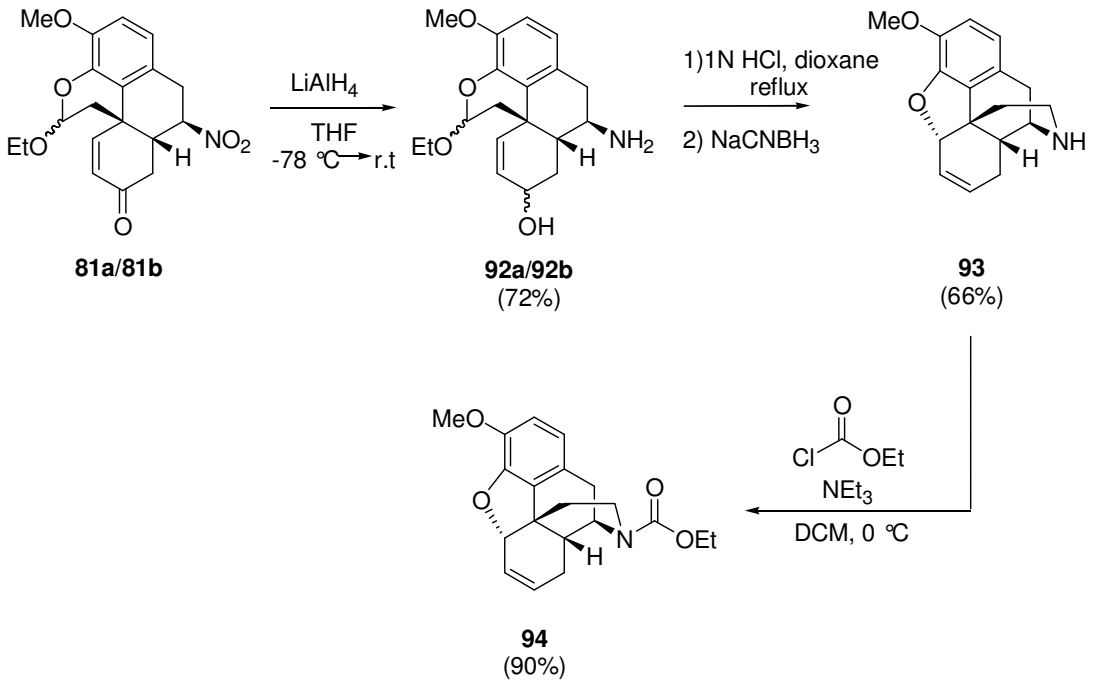
When nitroalkane **81b** was treated with freshly prepared aluminum amalgam in methanolic THF,[59] the hydroxylamine **90b** was obtained in 75% yield, Scheme 1.29. Hydroxylamines are known to undergo condensations with aldehydes to produce nitrones. When the hydroxylamine **90b** was subjected to acid hydrolysis, nitrone **91** was obtained as the sole product of the reaction. This fortuitous result implied that not only was the hydrolysis-amination strategy feasible, but an S_N2' attack of the free phenol on the allylic alcohol moiety could also lead to the intended furan ring closure and thus generate the core skeletal structure of morphine.



81b **90b** (75%) **91**

Scheme 1.29. Cyclization of hydroxylamines **90a/90b** under hydrolysis conditions.

The above result obviated the need to retain the enone functionality which had so far been crucial for the E-ring formation. We proceeded to reduce the nitroalkanes **81a/81b** to the primary amine using lithium aluminum hydride, which would also reduce the enone to an allylic alcohol. On treating the primary amines **92a/92b** to aqueous acid in the presence of sodium cyanoborohydride,[60] complete conversion to the pentacylic secondary amine **93** ensued and, the desired product **93** was obtained in a yield of 66%.

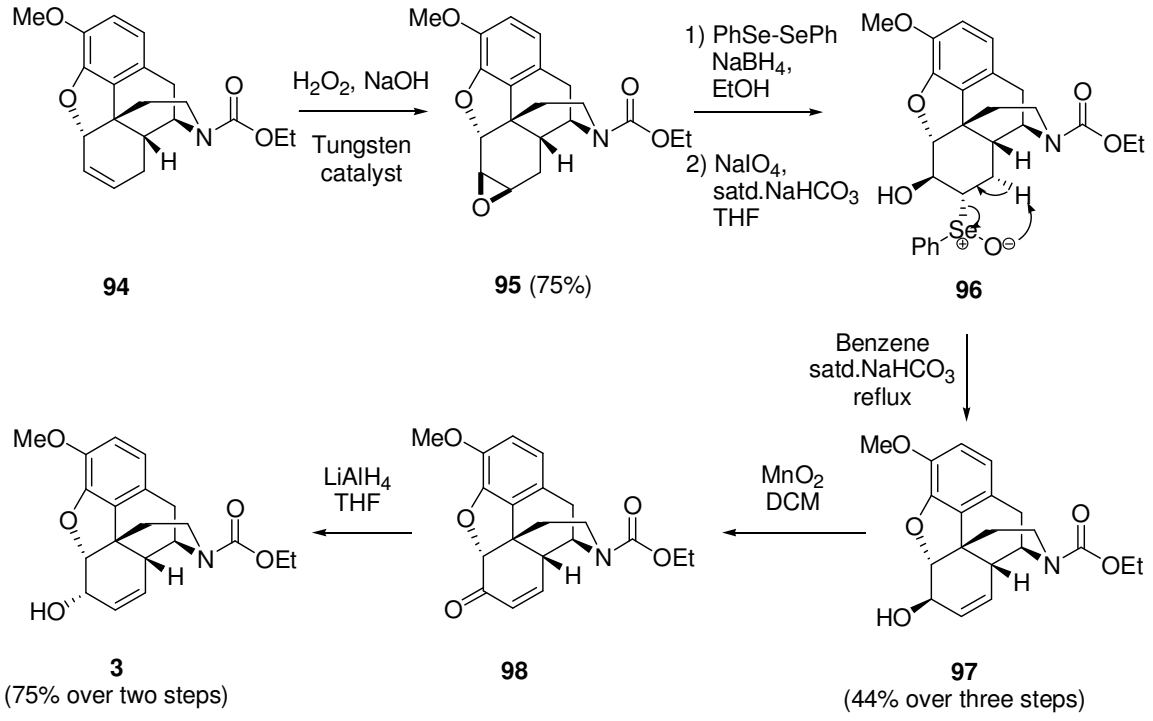


Scheme 1.30. Hydrolysis-reductive amination of the amines **92a/92b** and completion of a formal synthesis.

Upon treatment of the secondary amine **93** with ethylchloroformate, the ethylcarbamate **94** was obtained in 90% yield. The ethylcarbamate **94** had previously been synthesized in Taber's (2002) synthesis of morphine.[39] Compound **94** was identical in all respects to the data published in the manuscript. This completed a formal synthesis of morphine employing the idea of intramolecular phenolate alkylation to generate the quaternary center of the molecule.

1.2.5 C-ring oxidation

In Taber's synthesis of morphine, the ethylcarbamate **94** had been subjected to epoxidation followed by ring-opening with sodium phenylselenide, Scheme 1.31 and, rearrangement of the selenoxide **96** to the allylic alcohol **97**. The overall yield for the transformation was low and since most traditional epoxidation conditions had failed to epoxidize the molecule, the epoxidation had only been possible with the use of a special tungsten catalyst. Moreover, the β-epoxide **95** eventually required stereochemical inversion at C5 *via* oxidation of the incorrect allylic alcohol **97** to codeinone **98** before a final $LiAlH_4$ reduction to produce codeine **3**. This correction protocol is ubiquitous in the morphine area due to lack of methods that can functionalize the C ring from the sterically hindered α-face of the molecule.

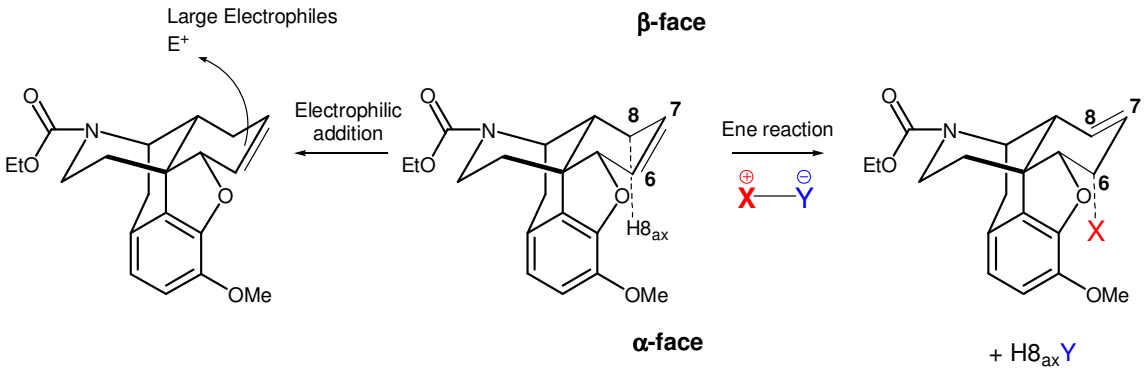


Scheme 1.31. Taber's strategy for the C-ring oxidative transposition.

Since the rationale for not attempting a classical oxidative transposition of the $\Delta^{6,7}$-alkene had not been provided in Taber's report, it was decided that in the course of this study an independent exploration of other alternatives for the oxidative transposition of the $\Delta^{6,7}$-alkene to the $\Delta^{7,8}$-double bond should be explored.

The molecular model of the ethylcarbamate reveals certain unique features regarding the sterics of the system, represented in Scheme 1.32. As is evident, the α-face of the molecule is sterically encumbered while the β-face is relatively unhindered. Any conformational change in this pentacyclic ring system is expected to be significantly cumbersome, and arguably, the molecule is locked in this form. Most large electrophiles would thus be expected to approach the alkene from the β-face.

Conversely, an ene reaction of small dipolar molecules would require an axial proton during the rearrangement, and hence, they would have to approach the alkene from the bottom face. Thus the loss of the H8 axial proton would not only rearrange the $\Delta^{6,7}$-double bond to the $\Delta^{7,8}$-double bond, but would introduce the electrophile at the C6-α-position, which is the required stereochemistry at C6.



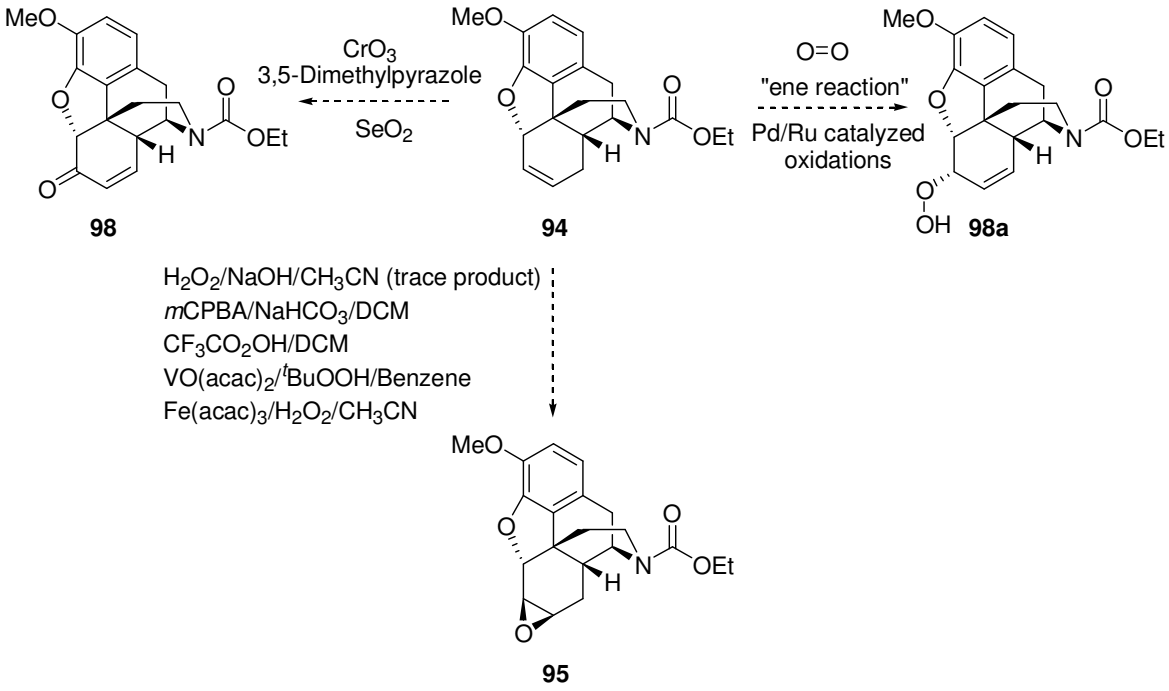
Scheme 1.32. Predicted approach of electrophiles onto the alkene of ethylcarbamate **94**.

Singlet oxygen is well known to engage in ene-reactions with alkenes.[61] The ene-reaction was expected to proceed with axial approach on the α-face of the alkene and produce the hydroperoxide **98a**, Scheme 1.33. Singlet oxygen for these reactions was generated using a mercury lamp and sensitizers such as tetraphenylporphyrin and Rose Bengal. However, the reaction only returned an intractable mixture of products. When palladium and ruthenium catalyzed Wacker-type oxidations were attempted, starting material was fully recovered.[62]

The ethyl carbamate **94** was treated with CrO_3-3,5 dimethylpyrazole, a reagent combination well known to oxidize alkenes to enones (with alkene transposition).[63] The reaction resulted in severe decomposition of the material. Similarly when selenium dioxide was used, extensive decomposition occurred.[64]

Since, ene-reaction type oxidation conditions had failed to induce the predicted rearrangement, other methods to functionalize the alkene were explored. Epoxidation of the ethylcarbamate **94** using mCPBA and trifluroperaceticacid led to extensive degradation of the starting material.[65] Epoxidations with hydrogen peroxide and *t*-butylhydroperoxide using oxo-Vanadium complexes and iron (VI) complexes as catalysts failed as well.

All of the hyper-reactivity of this substrate to these oxidations can be attributed to the presence of the highly electron-rich aromatic ring, which is expected to be quite susceptible to oxidation. A summary of the various oxidation conditions is presented in Scheme 1.33.

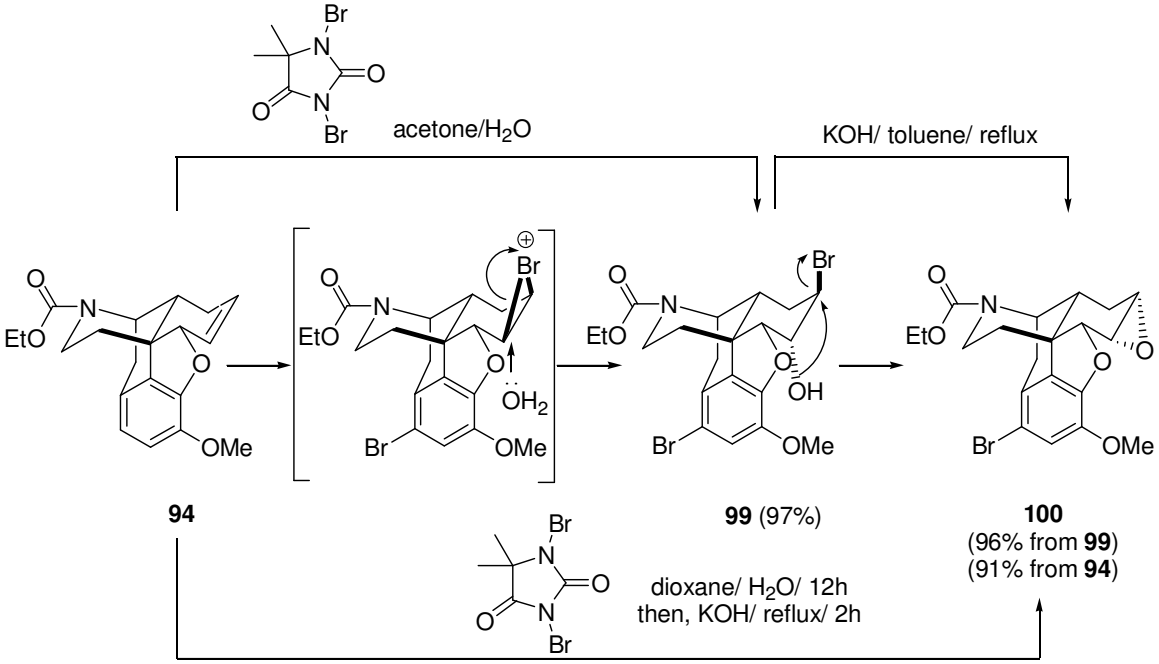


Scheme 1.33. Attempted oxidative transformations of the alkene.

A well established protocol in steroidal chemistry for the functionalization of the sterically hindered β-face, is to employ bromohydrin formations.[66] The large bromonium ion approaches the alkenes in such molecules from the less sterically encumbered (α-face in case of steroids) and opens the *epi*-bromonium ion to a bromohydrin. Subsequent treatment with base forms an epoxide on the β-face of the molecule.

When the ethylcarbamate **94** was treated with dibromohydantoin in aqueous THF, the bromohydrin **99** was obtained in 97% yield, Scheme 1.34. As speculated earlier, the first product of the reaction was indeed the bromination of the electron-rich aromatic ring and complete conversion to the bromohydrin was only seen after 12h. The bromohydrin was treated with solid KOH in toluene and heated at reflux for 2 h, after which complete

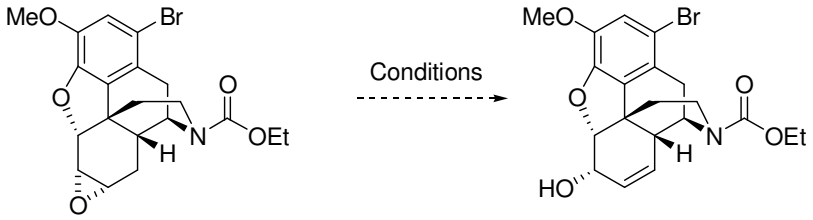
conversion to the epoxide **100** was seen. Thus, the initially formed β-*epi*-bromonium ion is first opened by axial attack of water at C6, to produce the bromohydrin **99** with the stereochemistry depicted. This is subsequently closed to an α-epoxide. The two steps can be combined into a one-pot procedure when aqueous dioxane is used for the first step. After complete conversion to bromohydrin **99** has occurred, KOH is added to the flask and heated to reflux to produce epoxide **100** in 91% yield.



Scheme 1.34. Epoxidation *via* bromohydrin formation.

In Taber's synthesis of morphine, the α-epoxide had been treated to sodium phenylselenide and subsequently oxidized to the selenoxide and eliminated to the allylic alcohol, Scheme 1.31. However the report did not mention if traditional epoxide-allylic

alcohol rearrangement conditions had been attempted. With this idea in mind, the epoxide **100** was treated with Al(^{i}PrO)$_3$ in refluxing toluene, a well known method to induce this rearrangement, Scheme 1.35.[67] However, no allylic alcohol was seen even after several days at reflux, (Table 1.01). Similarly, when Ti(^{i}PrO)$_4$ was used, no rearrangement product was observed. Use of Lewis acid activators like TMSOTf and TIPSOTf and BF_3.OEt in the presence of a base (DBU) did not induce the rearrangement.[68] Harsher conditions like DBN in refluxing xylenes and increasing the temperature to over 200 °C in sealed tube led to degradation of the compound to a complex mixture. This could be due to the fact that severe steric congestion on α-face of the molecule prevents the required geometry for these *syn*-elimination processes from being attained.



100 **101**

Scheme 1.35. Rearrangement of the epoxide **100** to the allylic alcohol **101**.

The use of lithium dialkylamides and harpoon bases such as metal-tetramethylpiperidides did not yield any allylic alcohol **101**.[69,70] When the epoxide opening was attempted using LDA and other lithium dialkylamides, no evidence of epoxide opening was seen by ^{1}H-NMR and a complex mixture was produced in the reaction. This could be due to degradation of the molecule caused by dehydrobromination of the bromoarene by LDA.[71]

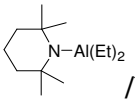
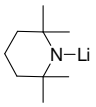
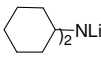
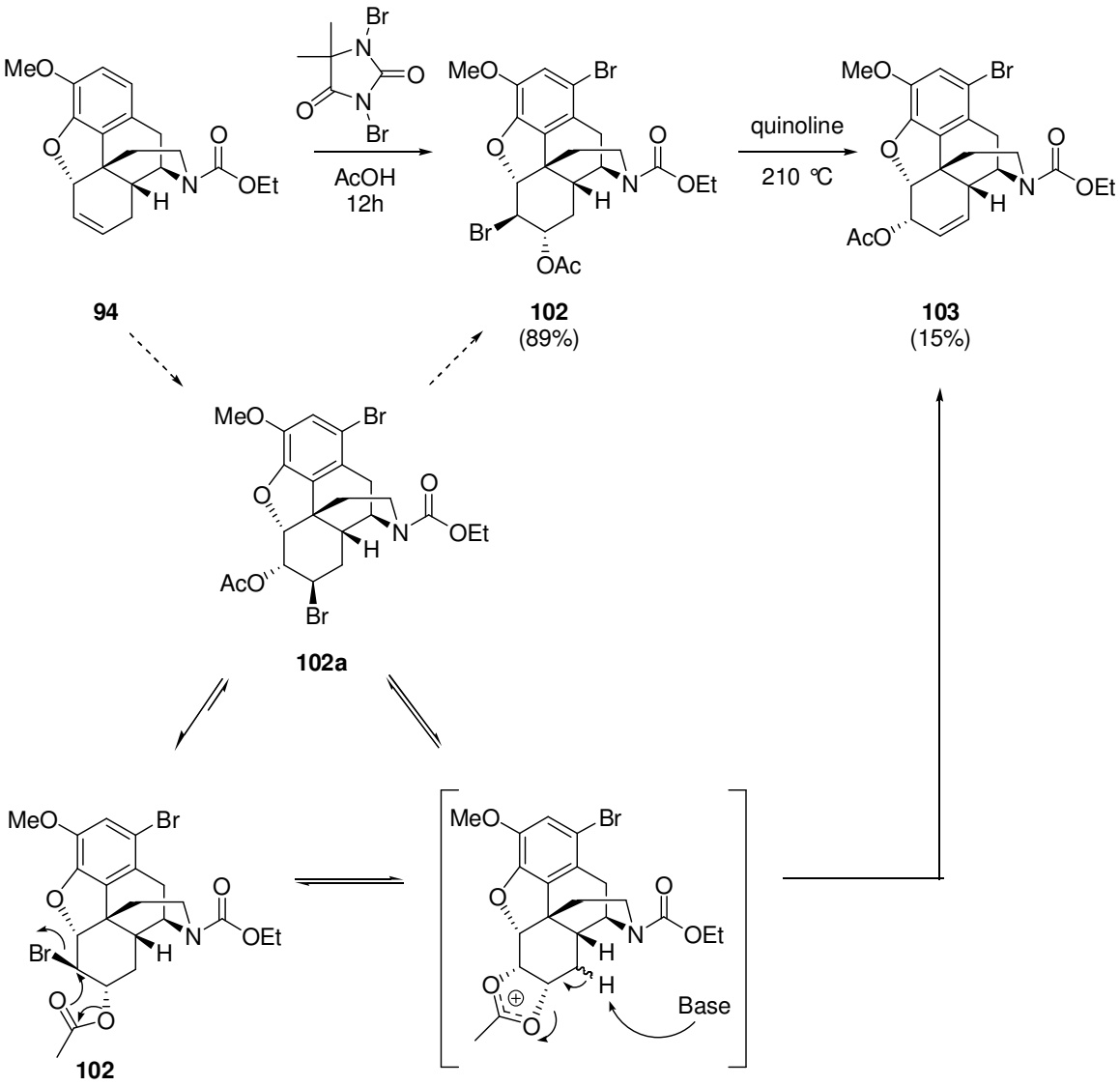
Condition	Result	Condition	Result
$Al(O^iPr)_3$/toluene/reflux	Recovered s. m.	LDA/THF/-78 °C	Complex mixture
$Ti(O^iPr)_4$/toluene/reflux	Recovered s. m.	$LiNEt_2$/THF/-78 °C	Complex mixture
DBU/ benzene/reflux	Recovered s. m.	$^iPr_2NMgBr$/THF/0 °C	Complex mixture
DBU/TMSOTf/benzene/ reflux	Complex mixture	 /benzene/0 °C	Complex mixture
DBN/xylenes/ sealed tube/ 200 °C	Complex mixture	 /THF/0 °C	Complex mixture
KH/ THF/sealed tube 140 °C	Recovered s. m.	 / THF/ -78 °C	Complex mixture

Table 1.01 Conditions attempted to convert the epoxide **100** to the allylic alcohol **101**.

The expected base-mediated epoxide opening had failed to achieve the desired rearrangement to the allylic alcohol **101**. As stated earlier, this was believed to be due to the steric hindrance on the α-face which prevented the *syn*-geometry required for such an elimination from being attained. An *anti*-elimination pathway could potentially be more favored.

With this idea in mind, we explored other alternatives to the functionalization of the alkene using the bromohydrin formation concept. When the ethylcarbamate **94** was treated with 1,3-dibromo-5,5dimethylhydantoin in acetic acid, the product of the reaction the acetoxy-bromide **106**, was obtained in 89% yield, Scheme 1.36. This compound was crystalline and, the X-ray structure (Figure 1.04) revealed that the acetate group was at the C7α position and the bromide was in the C6β position. At first, it would seem like the

observed product is contrary to what is expected from an axial opening of the *epi*-bromonium ion (Scheme 1.34). However, it is reasonable to assume that the initial product could indeed be the expected axial opening product **102a**, and this subsequently rearranges to the observed product **102** under equilibrating conditions.



Scheme 1.36. Neighboring group participation assisted dehydrobromination.

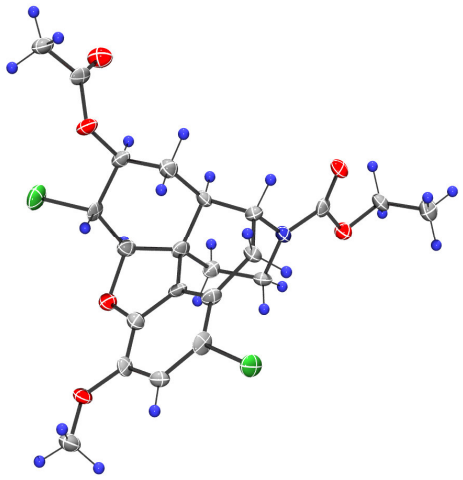


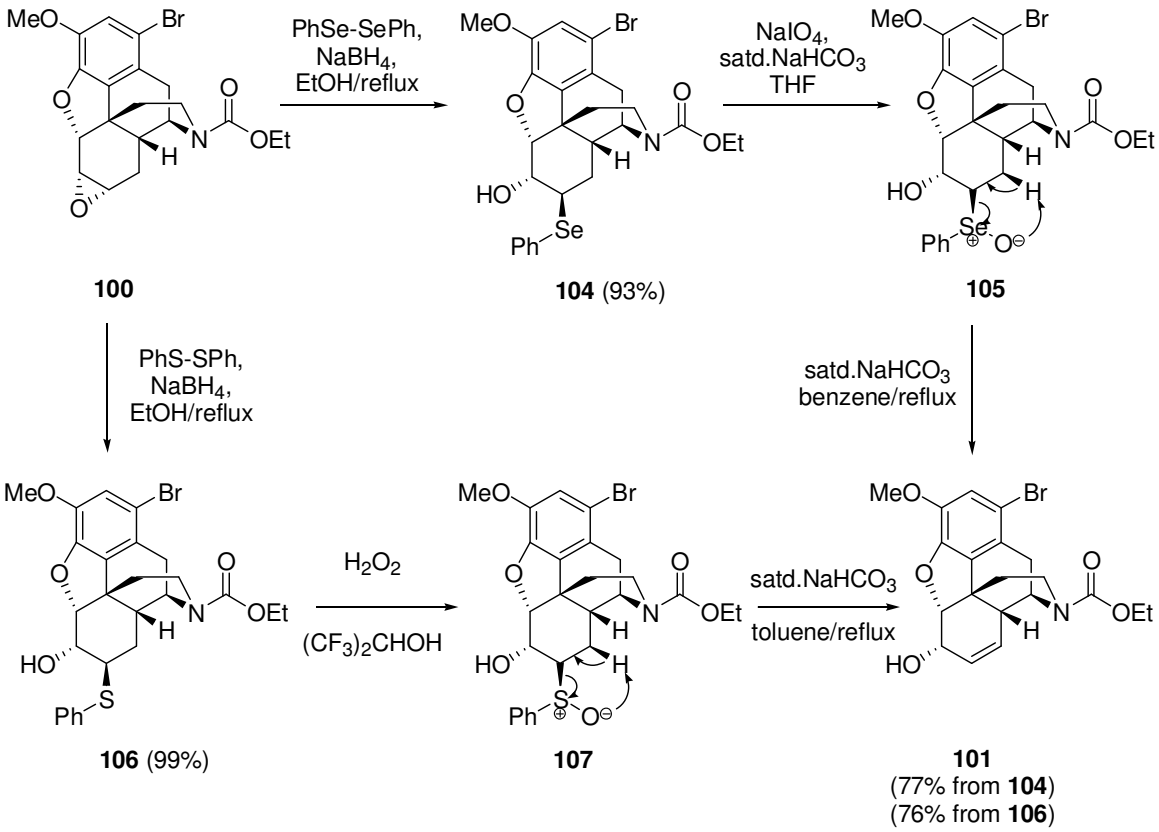
Figure 1.04 ORTEP representation of acetoxybromide **102**.

That the observed regiochemistry of the acetoxybromide **102** is contrary to the predicted regiochemistry (**102a**), should have no bearing on the dehydrobromination reaction. Both would form the same acetoxonium intermediate *via* assistance from the α-acetoxy group. Treatment of compound **102** with silver acetate in benzene was expected to form the allylic acetate **103** *via anti*-elimination. The soft Ag^+ counterion would assist the departure of the bromide. Neighboring group participation from the C7-acetate moiety, would then form the stable acetoxonium intermediate which could collapse to the allylic acetate. However, only a trace of the allylic acetate **103** was obtained from this reaction. When the acetoxy-bromide **102** was heated with excess DBU in refluxing xylenes, only a trace of the allylic acetate **103** was observed, accompanied by extensive decomposition of the substrate. When compound **102** was heated in quinoline at 210 °C, the allylic acetate was obtained in about 15% yield. The high temperature required for the

reaction and low yield obtained from it made it impractical to pursue this reaction any further.

Owing to the failures of various methods to effect rearrangement of the epoxide **100**, it was decided that the previously demonstrated protocol established by Taber would be applied to the molecule.[39] On treating the epoxide **100** to sodium phenyl selenide (freshly prepared by the reduction of diphenyl diselenide with sodium borohydride) 93% yield of the selenide **104** was obtained, Scheme 1.37. Subsequent oxidation using $NaIO_4$ and elimination of the isolated selenoxide **105** under basic conditions in refluxing benzene, produced complete conversion to the allylic alcohol **101**.

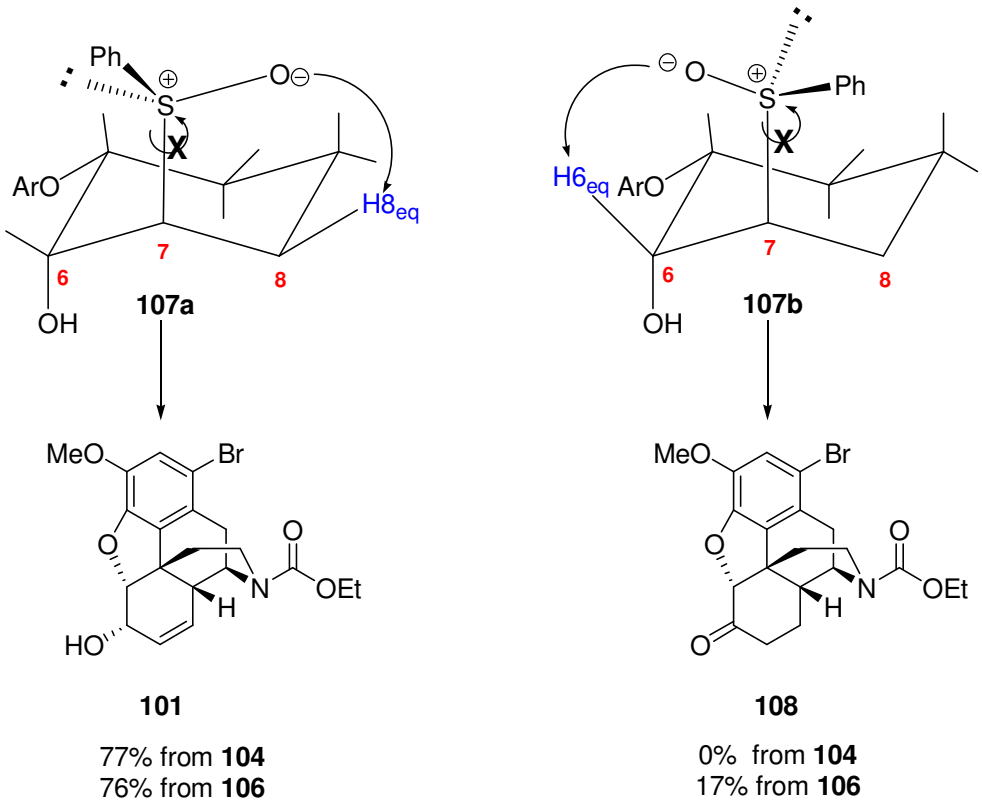
The use of selenide on larger scales did not portend well for scale up, particularly with regards to the toxicity associated with such compounds and it was thought best to explore a less toxic sulfur analogue. The epoxide opening was performed using freshly prepared sodium phenylsulfide. However, the subsequent oxidation with $NaIO_4$ did not produce any sulfoxide. The use of hydrogen peroxide in hexafluroisopropanol, a method which reputedly prevents over-oxidation of the initially formed sulfoxide to the sulfone,[72] was attempted. Isolation of the sulfoxide **107** and elimination produced the allylic alcohol in 76% yield. It is worth mentioning here, that no the sulfoxide elimination did not occur in refluxing benzene and the elimination required a higher temperature. Hence, the change of the solvent to toluene was imperative.



Scheme 1.37. Epoxide opening and oxidation-elimination to allylic alcohol **101**.

The ^{1}H-NMR spectrum of the crude product obtained in the sulfoxide elimination showed two signals in the aromatic region in the ratio 1:4. This was surprising, because no change in the aromatic region would be expected under these reaction conditions. On close examination it was found that a few other signals in the aliphatic region of the spectrum, showed unexpected peaks in the same molar ratio. It was concluded that the product must therefore be a mixture of two compounds. Mass spectroscopy data revealed that the product had the same elemental composition as the allylic alcohol. Further evidence was obtained from the ^{13}C-NMR spectrum, which showed a peak at δ = 200,

indicating the presence of a saturated carbonyl group in one of the compounds in the mixture, along with doubling of various other signals. IR spectroscopy confirmed this observation.



Scheme 1.38. Elimination pathways for the diastereomeric sulfoxides **107a/107b**.

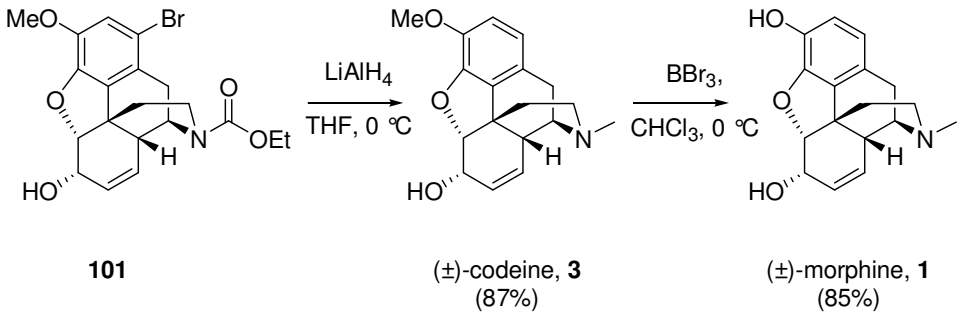
Collating all of the aforementioned spectral evidence, it was established that the by-product was in fact the saturated ketone **108** formed during the oxidation-elimination sequence performed on the phenylsulfide **104**, Scheme 1.38. The two products can be explained from the fact that during the oxidation of the sulfide **106** to the sulfoxide two diastereomeric forms of the sulfoxide **107a/107b** are produced. In sterically unhindered systems, the elimination always proceeds away from the carbon bearing the hydroxyl

group by rotation about the C-S bond. The energy barrier for such rotation is usually significantly lower than the energy required for rehybridization at the hydroxyl bearing carbon.

However, in this molecule, such a rotation would require the phenyl group to pass over the β-face of the C-ring. This in all probability is much more energetically demanding than the energy required for rehybridization. The diastereomeric ratio of the two sulfoxides formed during oxidation would hence determine the ratio of the two products formed in the [2,3]-sigmatropic rearrangement. The selectivity in case of the selenoxide can be explained by the fact that the length of the C-Se bond is higher by approximately 20 pm. than the C-S bond and hence rotation about this bond is expected to be less sterically demanding, which is probably the reason why both the selenoxides **105a/105b** produce the allylic alcohol product **101**, exclusively.

In an effort to alter this ratio in favor of the desired sulfoxide, the oxidation was performed at 50 °C. This increased the ratio of the ketone to allylic alcohol from the previous 1:4 (23 °C) to 1:5. When the oxidation was carried out at 0 °C, the ratio was 1.9: 1. Thus, it was clear that appropriate conditions could alter this ratio significantly, and it might even be possible to achieve the elimination without formation of the side-product by changing the alkyl group on the sulfur to a group smaller than a phenyl.[73]

All that remained to complete the synthesis of codeine, was to remove the aromatic bromide and convert the carbamate to the N-CH_3 group. Lithium aluminum hydride is known to effect the substitution of the aromatic bromide with a hydride in the morphine system as far back as Gates' first total synthesis of the molecule.[19] Similarly, the conversion of the carbamate to the N-Me has also been performed on this molecule by using $LiAlH_4$. Treatment of the allylic alcohol **101** with lithium aluminum hydride at 0 °C for 6h produced codeine in 87% yield, Scheme 1.39.



101 (±)-codeine, **3** (87%) (±)-morphine, **1** (85%)

Scheme 1.39. Reduction and completion of total synthesis.

Finally, treatment of the racemic codeine **3** with BBr_3 in chloroform,[74] effected the demethylation of the aromatic methoxy group to produce morphine in 85% yield. This completed the total synthesis of (±)-morphine employing for the first time an intramolecular phenolate alkylation strategy to generate the quaternary center of the molecule. The overall yield is 17% for the 14 step reaction sequence and this represents the shortest synthetic route to (±)-morphine.[75]

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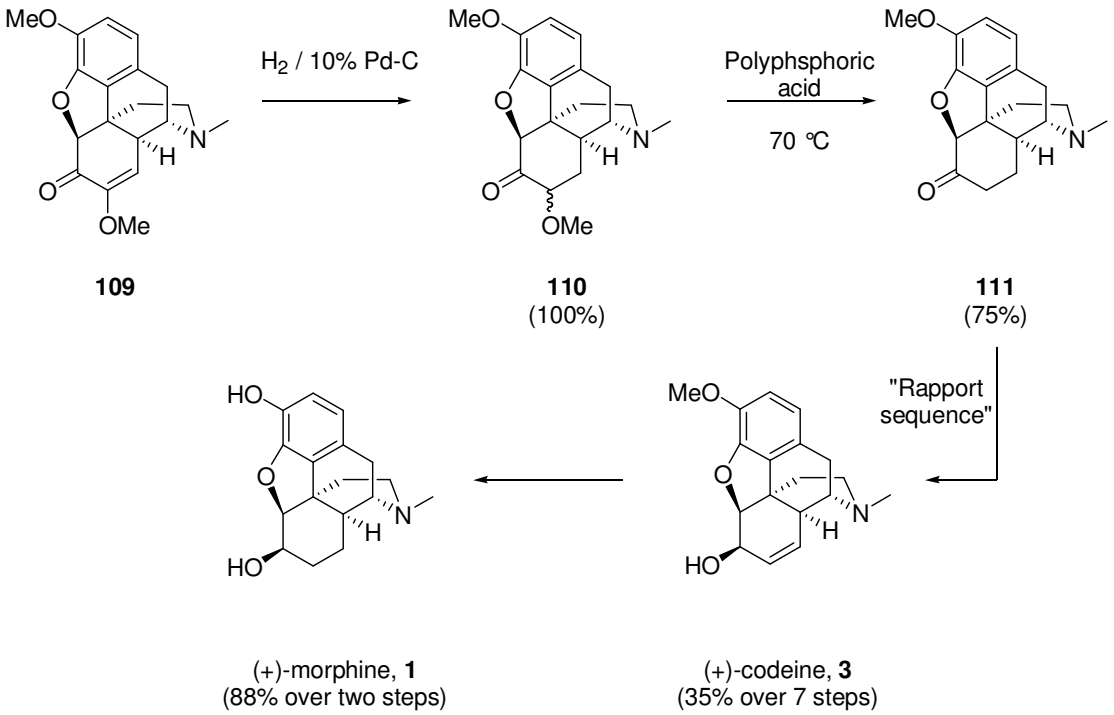
CHAPTER 2: TOWARDS AN ENANTIOSELECTIVE SYNTHESIS OF (-)-MORPHINE

2.0 INTRODUCTION

Pharmacological activity of the opiates is significantly dependent on the absolute configuration.[1] It was found that there are two classes of receptors that mediate the effects of morphine; the ones that are highly stereospecific and the ones that are less discriminatory. The ones that are stereospecific are receptors for the endogenous ligands, the endorphins, which mitigate pain, while the receptors of the second kind, which are less selective, are responsible for the hyper-reactive motor behavior induced by the opiates. For instance, (-)-morphine and naloxone (an opiate drug widely used to counter the effects of opiate overdose) block the receptors of the first kind, while they fail to bind to the receptors of the second kind. In contrast, (+)-morphine and dextromorphan, which do not bind to the receptors of the first kind, impart no analgesia. Instead (+)-morphine shows only the hyperexcitability that follows (-)-morphine administration, indicating that it binds to the second receptor. Dextromorphan in fact is not an analgesic and is used as a cough suppressant. It has been an ongoing quest of the pain-management industry to find analogues that are less addictive but equally analgesic and thus mitigate the negative effects of opiate administration.

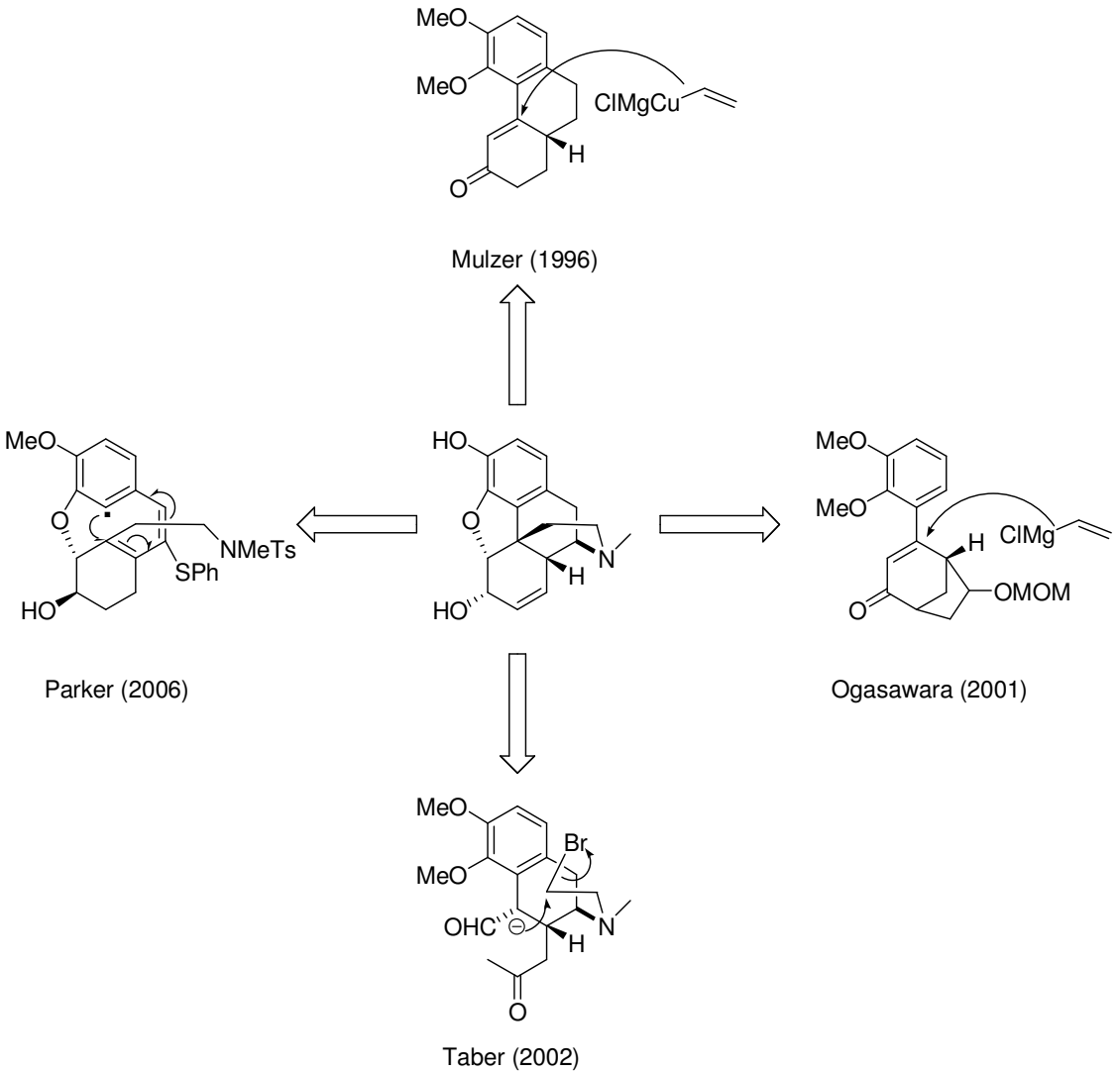
2.0.1 Previous strategies for the enantioselective synthesis of (-)-morphine.

Due to a lack of syntheses of morphine which are truly practical on large scales, a classical resolution is not a viable alternative to produce the unnatural (+)-isomer. The (+)-isomer, required for the previously mentioned biological studies, was synthesized from (-)-sinomenine (**123**). Sinomenine is a naturally occurring substance, structurally similar, but with opposite optical rotation of natural morphine, Scheme 2.01.[2]



Scheme 2.01 Conversion of (-)-sinomenine to (+)-morphine

The enantioselective synthesis of morphine, without the use of resolution, was first reported by Overman (1993)[3] and subsequently by White (1997)[4] and Trost (2002)[5]. These syntheses have been previously discussed in Chapter 1. The syntheses reported by Mulzer (1996),[6] Ogasawara (2001),[7] Taber (2002)[8] and Parker (2006)[9] require chiral resolution of an early intermediate and the diastereocontrol for all the other stereocenters is derived from the enantiomerically enriched intermediate, Scheme 2.02.



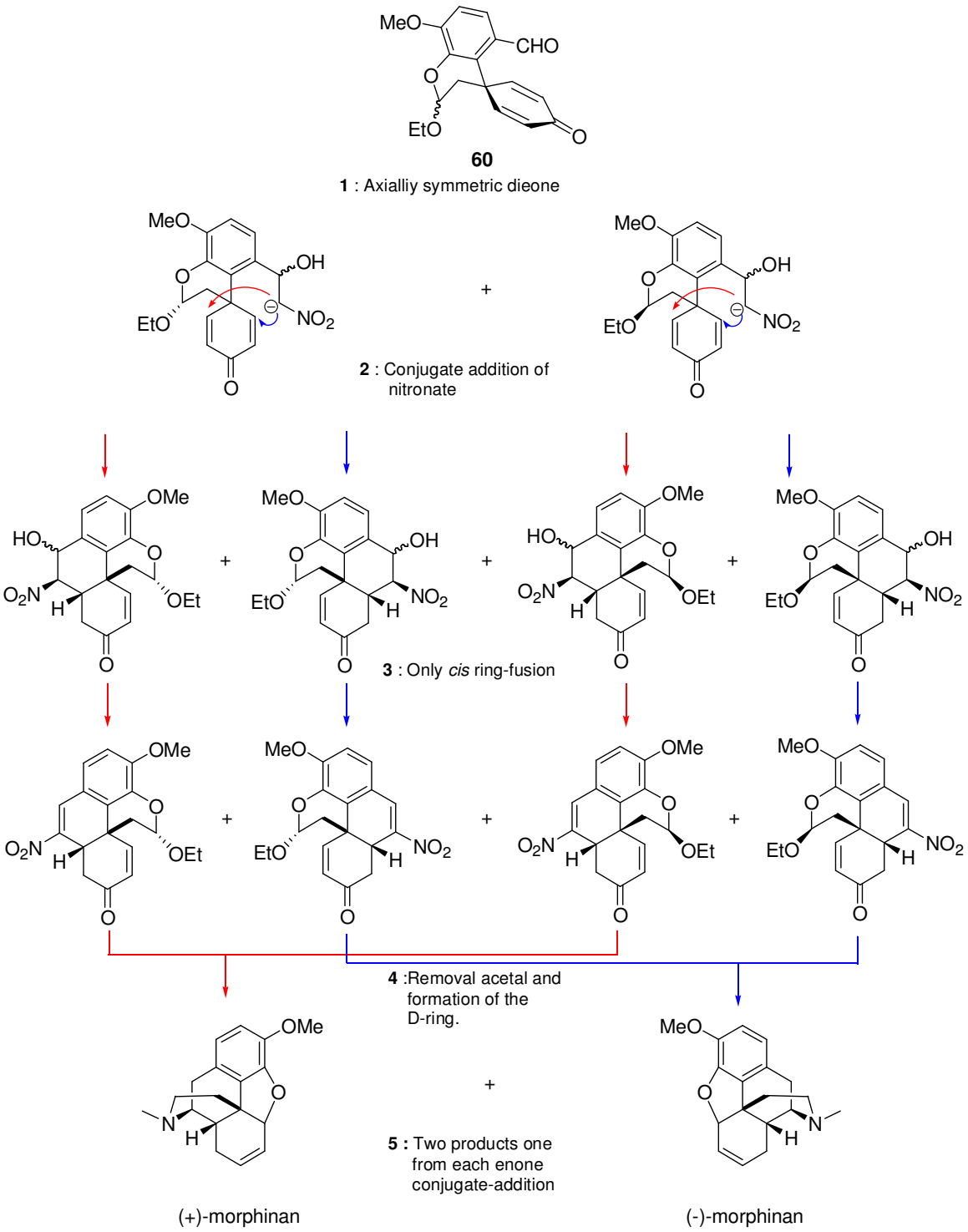
Scheme 2.02. Formation of the quaternary center in previous enantioselective syntheses.

2.2 RESULTS AND DISCUSSION

2.2.1 Strategy to achieve enantioselectivity in the system under study

Before outlining the synthetic strategy envisioned for achieving enantioselectivity in the system under study, it is important to note some key features of the dienone molecule, compound **60** (Scheme 2.03).

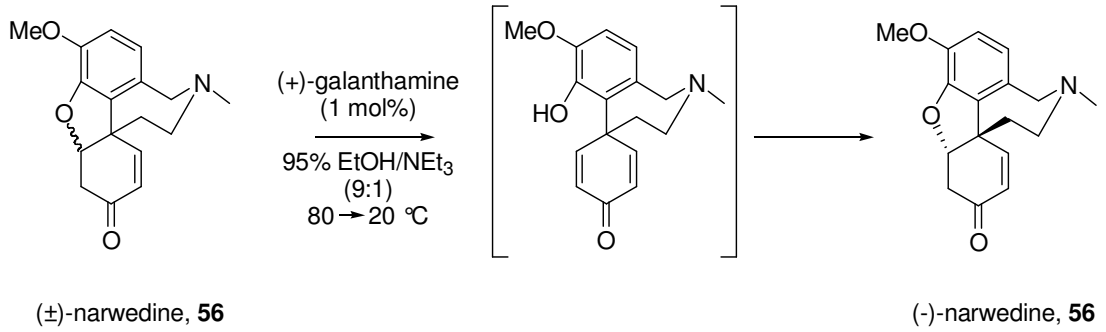
1) The dienone **60** is axially symmetric.
2) The stereochemistry at the quaternary center will depend upon which of the two enones is favored by the chiral catalyst towards conjugate addition.
3) The product of the nitroaldol reaction between the aromatic aldehyde and nitromethane results in **only** the desired *cis* ring-fusion product.
4) The product of the above reaction would result in a mixture of four isomers, two of which have the same stereochemistry about the chiral center, and the other two the opposite.
5) In the subsequent reactions, since the acetal stereocenter is destroyed by hydrolysis, the four isomers formed initially will now only be two, each with opposite stereochemistry at the quaternary center, i.e. enantiomers.
6) If the chiral catalyst system was indeed successful in biasing one enone over the other (i.e. one of the two colored pathways depicted in Scheme 2.03), the final outcome would be an enantiomerically enriched morphinan.



Scheme 2.03. Influence of the stereochemistry of conjugate addition on the final stereochemical outcome of the reaction sequence.

2.2.2 Dynamic resolution

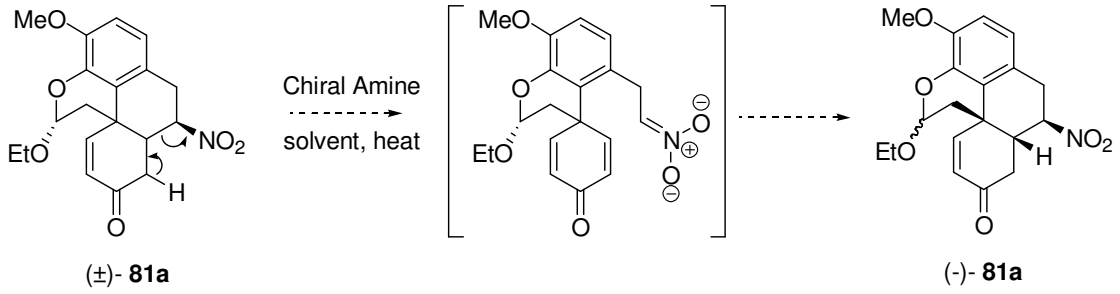
Our first idea to achieve enantioselectivity was loosely based on the dynamic resolution-type process, similar to the one used in the Ciba-Geigy method[10] for the resolution of narwedine by (-)-galanthamine, Scheme 2.04.



(±)-narwedine, **56** (-)-narwedine, **56**

Scheme 2.04 Ciba-Geigy dynamic resolution of (±)-narwedine.

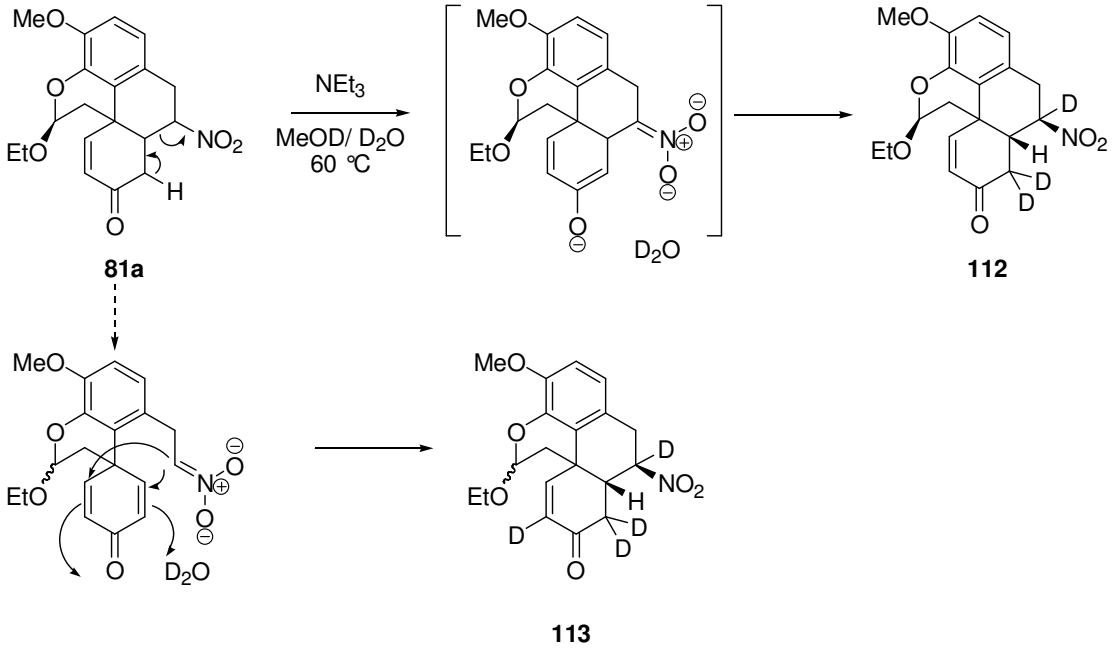
We had envisioned a similar set-up for the racemic nitroalkane **81a**, that, in the presence of a chiral base a retro-Michael reaction could generate the free nitronate which could add back onto a preferred enone and thus potentially enrich one of the enantiomers, Scheme 2.05.



(±)- **81a** (-)- **81a**

Scheme 2.05. Proposed dynamic resolution of nitroalkane **81a**.

In order to test if this hypothetical process is feasible, we carried out deuterium labeling studies. When the nitroalkane **81a** was heated with triethylamine in deuterated methanol and deuterium oxide for 12h, the trideuterated product **112** was observed by ^{1}H-NMR, Scheme 2.06. If the retro-Michael reaction had indeed taken place, the axially symmetric dienone would have resulted in deuterium incorporation at both the enone positions to give the tetradeuterated compound **113**. The presence of just the trideuterated compound in the product meant that the ring opening had not occurred as expected.



Scheme 2.06 Attempted ring-opening of the nitroalkane **81a**.

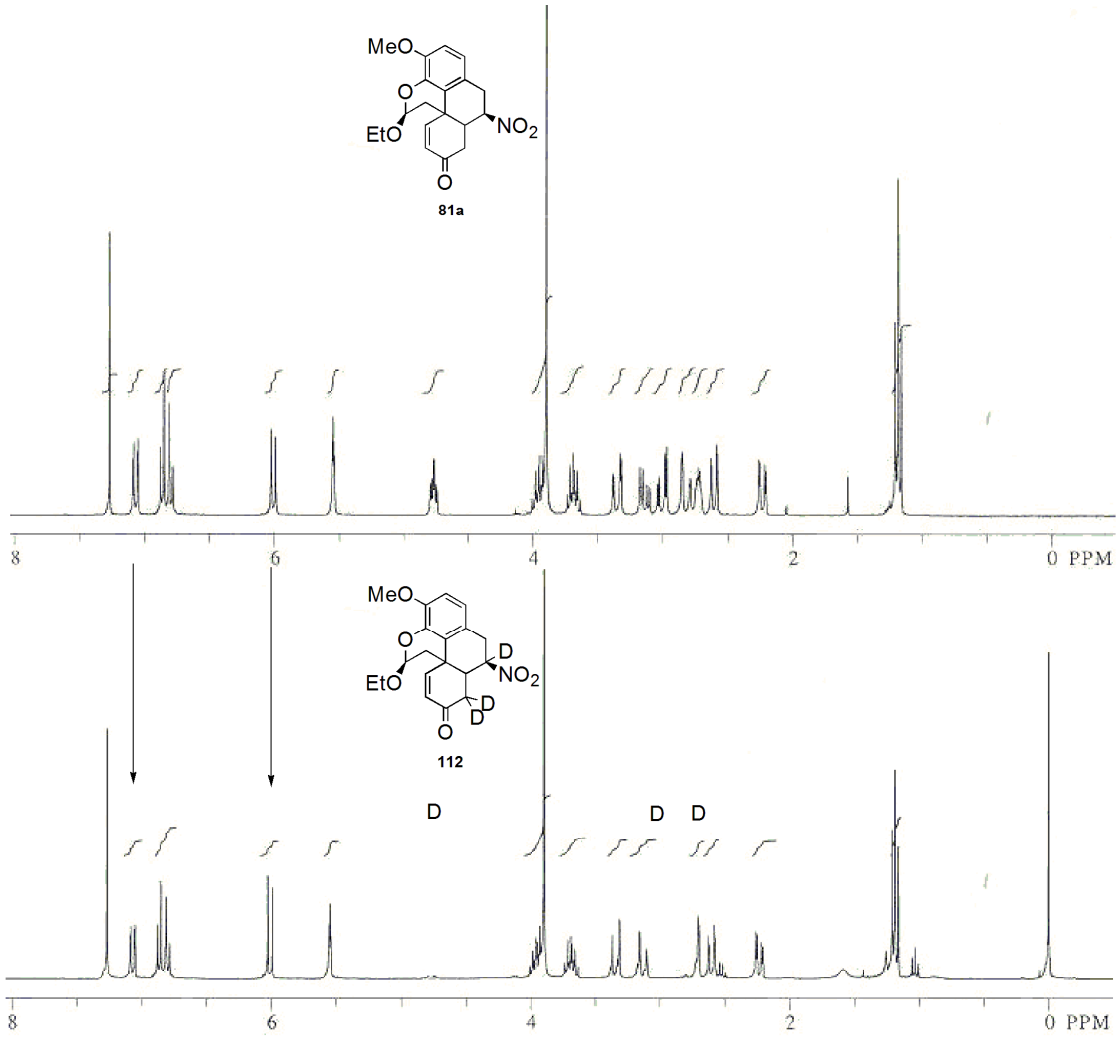
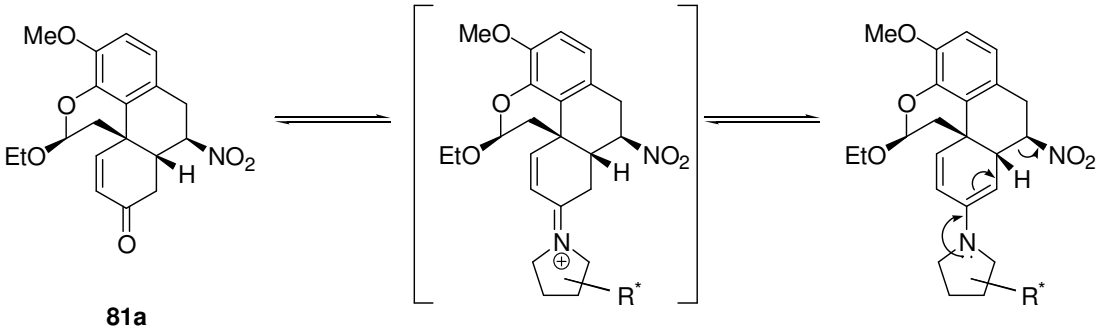


Figure 2.01. ^{1}H-NMR of the deuterated compound indicating the absence of deuterium incorporation at the enone position.

The addition of L-proline, which we had expected could form an enamine with the ketone in **81a** and facilitate the retro-Michael process (Scheme 2.07), showed no deuterium incorporation either. When this reaction was attempted using a mixture of pyrrolidine and acetic acid (catalytic) and heated in refluxing toluene, again no deuterium incorporation was observed. With this, the idea of attempting a dynamic resolution using a chiral base was abandoned. It was concluded that the retro-Michael reaction was probably too energetically demanding to be able to achieve the required reversible set-up.

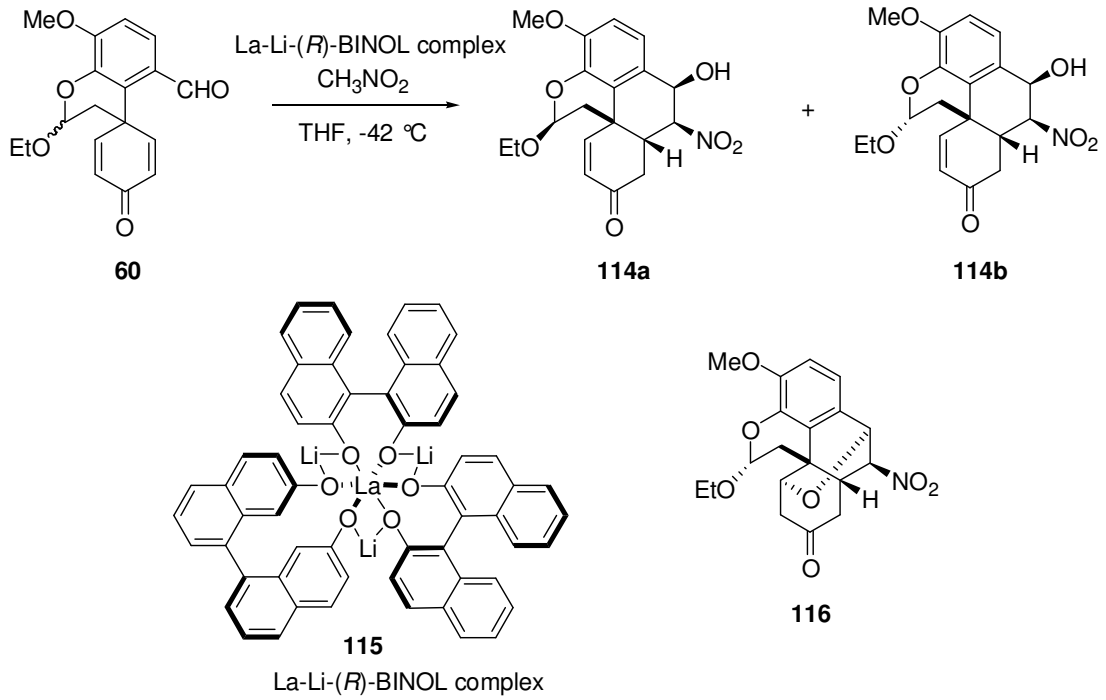


Scheme 2.07. Iminium activated retro-Michael reaction.

2.2.4 Enantioselective nitroaldol-conjugate addition reaction

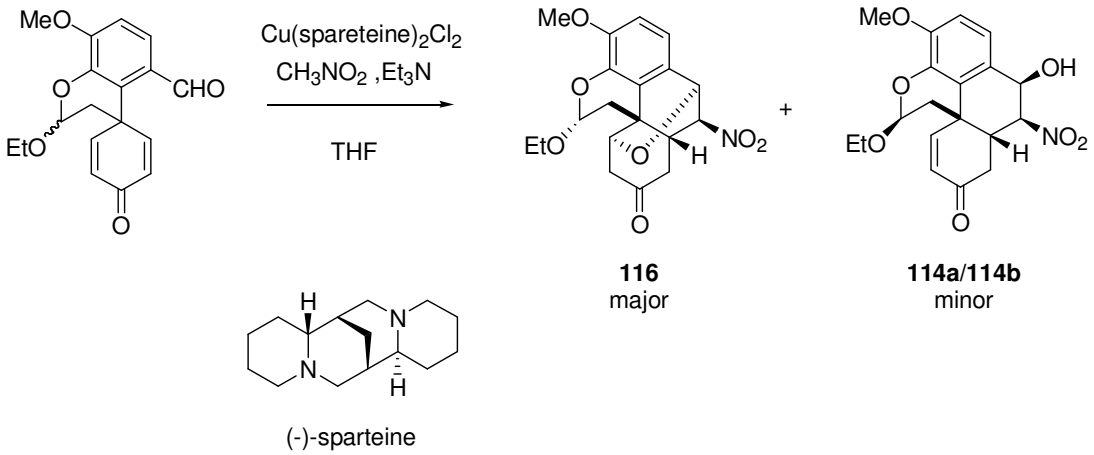
There are several methods available for the enantioselective nitroaldol reactions reported in literature and numerous reviews have been published on this topic.[11] Similarly, the enantioselective conjugate addition of nitroalkanes onto activated alkenes is also well precedented.[12] Although the substrate scope for these two classes of reactions is fairly wide, there are no definitive parameters established for making an educated choice of the catalyst. Our strategy required the conjugate addition step to be enantioselective, but we reasoned that since the nitroaldol reaction preceded the conjugate addition step, an enantioselective nitroaldol catalyst could provide an optically enriched nitroalcohol which in turn could be more selective to one of the two enones. Some catalysts are known to catalyze both, the enantioselective nitroaldol as well as the enantioselective conjugate additions of nitronates, and as a starting point we chose to explore such catalyst systems.[13]

Our first choice was the use of the Shibasaki heterobimetallic catalyst[14] (**115**, Scheme 2.08) which was prepared using the reported literature procedure.[15] Treatment of the dienone with the catalyst and nitromethane at -40 °C resulted in complete consumption of the dienone and the formation of several compounds (TLC). Two of the major products were found to be the desired nitroalcohols **114a/114b** and the other the nitroether **116**. Attempts at controlling the reaction to produce just the two desired products failed and hence the catalyst system was abandoned due to lack of selectivity.



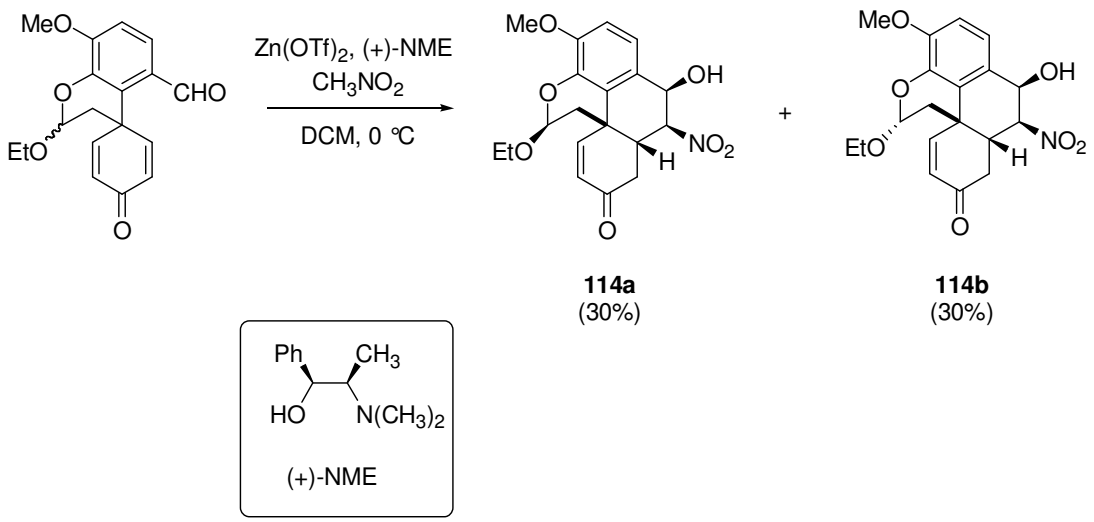
Scheme 2.08. Nitroaldol reaction with Shibasaki's (*R*)-LaLB catalyst.

Copper-sparteine complexes are also known to impart high enantiomeric excesses to nitroaldol reactions as well as conjugate additions of nitronates to enones.[16] The copper-sparteine complex was prepared under the reported conditions and subjected to the nitroaldol reaction. The predominant product under various reaction conditions was the cyclic nitroether **116** and this obviated any further exploration of this catalyst system, Scheme 2.09.



Scheme 2.09 Cu-sparteine catalyst in the nitroaldol reaction.

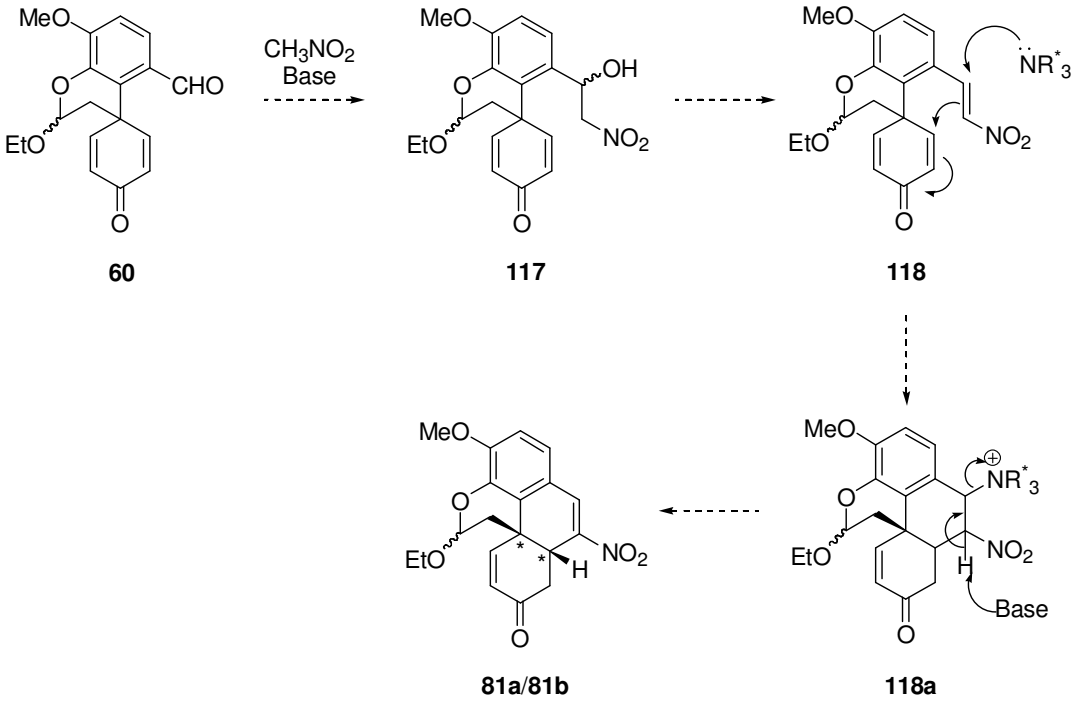
Zinc triflate in the presence of chiral 1, 2-aminoalcohols has been known to catalyze and exhibit a high degree of enantioselectivity in nitroaldol reactions.[17] Consequently, treatment of the dienone under the conditions depicted in scheme 2.10 gave 60% yield of the two nitroalcohols **114a/114b**. However, the two nitroalcohols showed no optical rotation; clearly there was no enantiomeric excess imparted to the molecule by the catalyst. When the solvent was changed to toluene instead of dichloromethane, less than 10% conversion occurred at 23 °C even after 4 days of stirring. When the same reaction was carried out at higher temperatures, complete conversion occurred, but several products corresponding to the various nitroalcohol isomers and the cyclized form were observed (TLC), rendering the catalyst system unusable for further investigation.



Scheme 2.10. Zn-NME catalyst system for the nitroaldol.

2.2.3 Isolation of uncyclized nitroalcohol

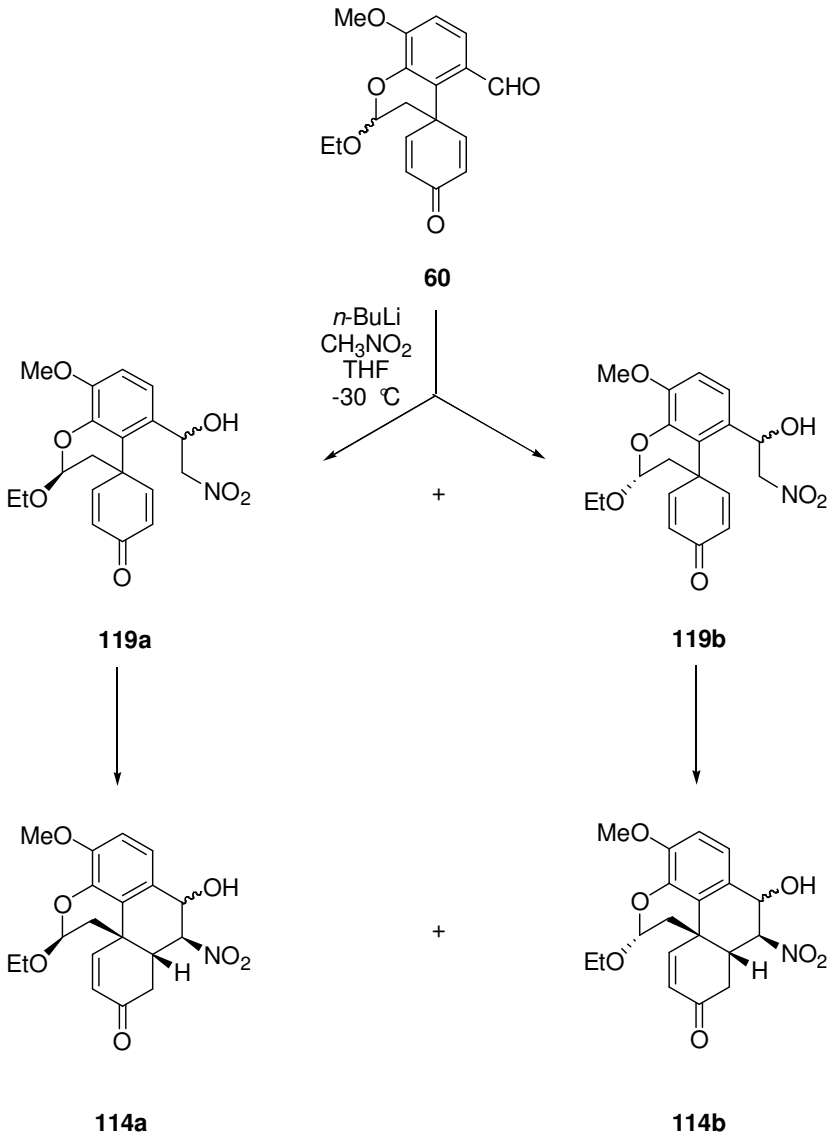
Before proceeding any further with the screening of other catalyst systems to achieve the intended enantioselective conjugate addition, we were interested in disengaging the two sequential steps that provide us with the desired nitroalcohol; i.e. isolation of the intermediate uncyclized nitroalcohol, before the conjugate addition could occur, Scheme 2.11. The uncyclized nitroalcohol **117** could then be dehydrated to the nitroalkene **118**, which would allow us to explore Baylis-Hillman type conditions using chiral tertiary amine /chiral phosphine to dictate the stereochemistry of the conjugate addition process.[18]



Scheme 2.11. Chiral Baylis-Hillman-type intramolecular coupling of the nitroalkene to the enone to set the stereochemistry at the quaternary center.

When a solution of the dienone **60** in THF was added to a suspension of *n*-butyllithium in nitromethane at -78 °C, initially, no conversion was observed. However, when the cooling bath was allowed to warm to -30 °C, two spots were observed by TLC analysis. The reaction mixture was quenched at this stage and the products were isolated using preparative TLC. ^{1}H-NMR of the two compounds isolated indicated that the aldehyde signal was no longer present, but the dienone signals were still seen, making it safe to assume that these were indeed the product of the first addition, the uncyclized nitroalcohols **119a/119b**, Scheme 2.12. However, ^{13}C-NMR of the products could not be obtained since under the mildly acidic conditions of the NMR solvent, $CDCl_3$, the two

compounds had cyclized to the corresponding cyclic nitroalcohols **114a/114b**. The products **119a/119b** rapidly cyclized under basic conditions too.



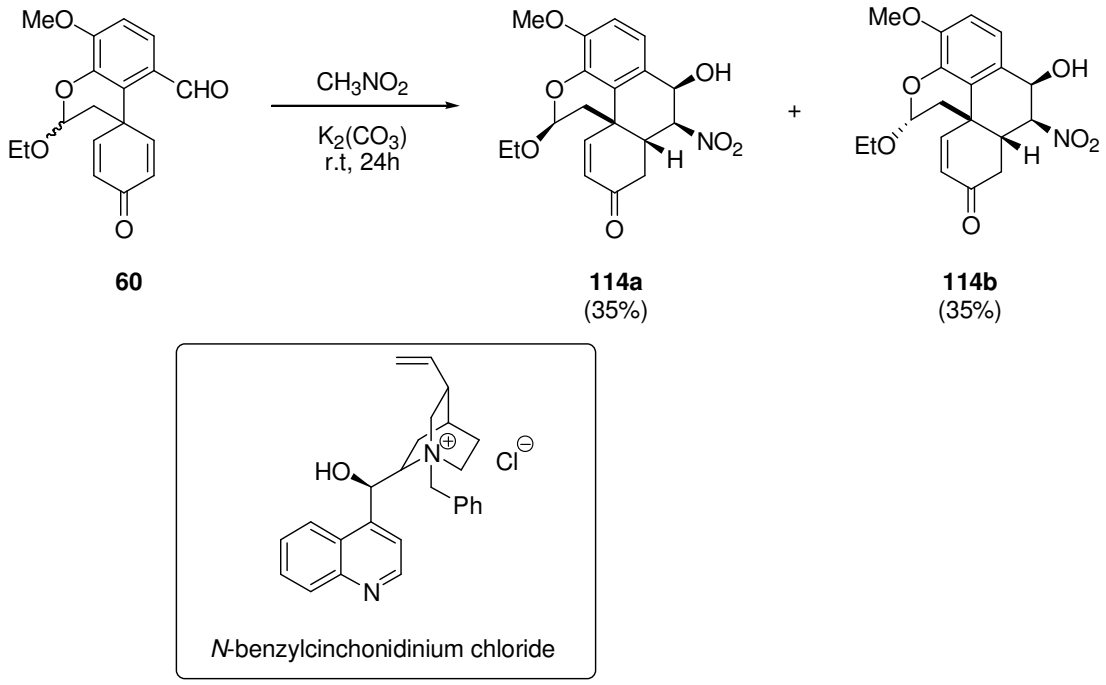
Scheme 2.12. Isolation of uncyclized nitroalcohols.

This was an important result, since it demonstrated that the initial products, the uncyclized nitroalcohols **119a/119b**, were susceptible to ring closure under both acidic and basic conditions and hence the idea of a dehydration without ring-closure was not viable. Secondly, since each of the products had given rise to a 1:1 mixture of the two cyclic nitroalcohols **114a/114b**, it implied that the stereochemistry at the benzylic position had no bearing on the selectivity of the enone face. Thus, it was critical that the focus be diverted from the enantioselective nitroaldol step to the enantioselective conjugate addition step in order to achieve any enrichment at the quaternary center.

2.2.4 Chiral phase-transfer catalysis

Chiral phase transfer catalysis has been a front runner in enantioselective organocatalysis and takes advantage of the fact that most phase transfer catalysts are water soluble, and the products can be easily separated due the biphasic nature of these systems. The first truly practical use of this methodology came from the Merck process group in 1984, in the alkylation of phenylindanone derivatives using *N*-alkylated cinchonine.[19] Since then, the idea has been extended to various transformations and the pool of available chiral phase transfer catalysts has increased manifold.

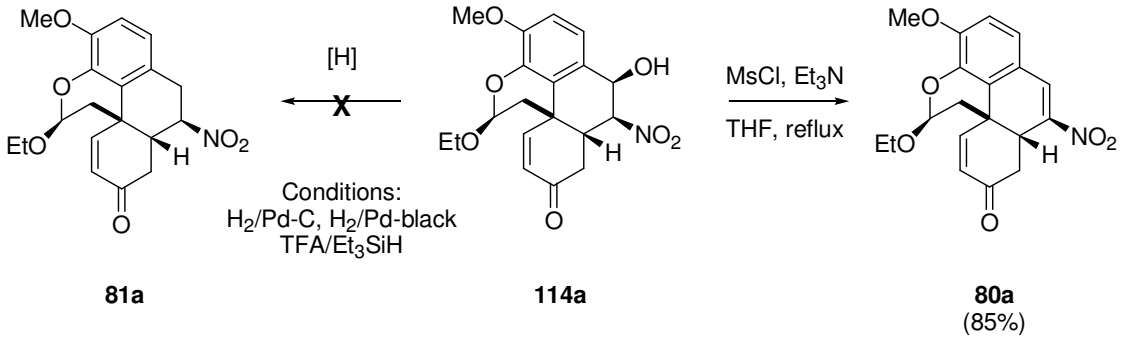
When the dienone **60** was treated with nitromethane and potassium carbonate using the catalyst *N*-benzylcinchonidinium chloride, complete conversion to the two nitroalcohols **114a/114b** was observed. The nitroalcohols individually showed a strong optical rotation indicating that the catalyst system had succeeded in inducing enantioenrichment to the molecules.



Scheme 2.13 Chiral phase-transfer catalyzed nitroaldol reaction

For the purposes of determining the enantiomeric excess (ee), it was thought prudent to convert the two isolated nitroalcohols **114a/114b** to a previously synthesized intermediate en route to the synthesis of morphine. First, the selective reduction of the nitroalcohol **114a** to the nitroalkane **81b** was attempted. However, various reductive conditions failed to effect the benzylic alcohol cleavage, Scheme 2.14.

Treatment of the nitroalcohol to methanesulfonylchloride and triethylamine converted the nitroalcohol **114a** to the corresponding nitroalkene **80a**. Thus the product of the enantioselective step could be introduced into the previously completed synthesis without having to make making any major changes to the overall synthetic design. The ee of the nitroalkene **80a** thus formed was found to be 27% by chiral HPLC using an ODH chiral column.



81a **114a** **80a** (85%)

Scheme 2.14 Conversion of the enantioenriched nitroalcohol **114a** to the previously synthesized nitroalkene **80a**.

With the success of the method in achieving a slight enantiomeric excess, optimization of the reaction conditions was initiated. First, a variety of carbonates were screened to effect the conversion. The bases Li_2CO_3, $MgCO_3$, $BaCO_3$ were found to be too unreactive towards the reaction, even at room temperature. Na_2CO_3, K_2CO_3, Cs_2CO_3 were found to be increasingly reactive (in that order) at room temperature. Since, it had been previously observed that the conjugate addition step was fast at higher temperatures (Scheme 2.12), the reaction would need to be conducted at a low temperature in order to facilitate higher selectivity during the conjugate addition. When the temperature of the reaction was lowered to 0 °C, Na_2CO_3 was unreactive and at -20 °C K_2CO_3 was found to be unreactive, even over long reaction times. Although Cs_2CO_3 was unreactive at -78 °C, it was reactive above -20 °C. Thus, the ideal bases for this reaction were found to be K_2CO_3 and Cs_2CO_3 and the optimal temperature range was -20 °C to 0 °C.

Entry	Base	Solvent	Temperature	Time	Enantiomeric excess (ee)
1	Cs_2CO_3	$MeNO_2$	0 °C	8h	27%
2	Na_2CO_3	$MeNO_2$	23 °C	48h	20%
3	K_2CO_3	$MeNO_2$	23 °C	24h	20%
4	K_2CO_3	$MeNO_2$/Toluene 1:1	23 °C	48h	50%
5	Cs_2CO_3	$MeNO_2$/Toluene 1:10	-78 °C	24h	No reaction
6	Cs_2CO_3	$MeNO_2$/Toluene 1:10	-20 °C	24h	80%
7	Cs_2CO_3	$MeNO_2$/Toluene 1:20	-20 °C	72h	50%

Table 2.01 Optimization of the reaction conditions for the *N*-benzylcinchonidinium chloride catalyzed enantioselective nitroaldol reaction. The ee's reported are for the nitroalkene **80a** derived from the corresponding nitroalcohol **114a** (Scheme 2.14).

In neat nitromethane and using K_2CO_3 as the base, the ee observed for the nitroaldol product was 20%. Under identical conditions Cs_2CO_3 imparted an ee of 27%. When the reaction was carried out in a 1: 1 mixture of nitromethane to toluene using K_2CO_3 as the base, the ee improved to 50%. Clearly, lower temperatures and increase in toluene concentration were inducing greater selectivity in the reaction. When the solvent system was changed to 1: 10 nitromethane to toluene using Cs_2CO_3, the ee improved to 80%.

The dramatic improvement in ee with the lowering of the polarity of the solvent system (increase in toluene concentration) can be attributed to two factors.

1) The non-polar interactions between the positively charged catalyst and toluene would enhance the binding of the catalyst to the nitronate anion, during catalysis.
2) Reduction in the equivalents of nitromethane would reduce the possibility of a background reaction, one in which the nitronate is disengaged from the chiral catalyst.

It was found that the highest enantiomeric excess was obtained when the nitroaldol reaction was performed using cesium carbonate as the base in a solvent mixture of nitromethane and toluene in the ratio 1:10, at -20 °C. The reaction took 24h for complete conversion of the dienone to the two nitroalcohols **114a/114b**, and the enantiomeric excess observed was 80% for each of the diastereomers.

Further optimization was beyond the purview of the present study. The isolation of the two nitroalkenes **80a/80b** each with an ee of 80%, was deemed satisfactory for the purpose of a "proof-of-concept" investigation. However, it remains to be seen if the stereochemistry at the quaternary center, imparted by the phase-transfer catalyst *N*-benzylcinchonidinium chloride, is identical to that of natural morphine. If otherwise, *N*-benzylcinchoninium chloride, the commercially available antipode of this catalyst, should in principle impart the opposite stereochemistry.

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CHAPTER 3: SYNTHESIS OF (-)-GALANTHAMINE

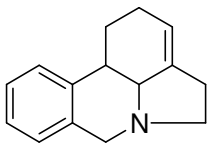
3.0 INTRODUCTION

The Amaryllidaceae are a family of herbaceous, perennial and bulbous flowering plants included in the monocotyledonous order Asparagales and take their name from the genus Amaryllis. The roughly 1100 species of plants in this family are mostly deciduous, rarely shrubby or treelike plants, often with bulbs, and rarely, with rhizomes.

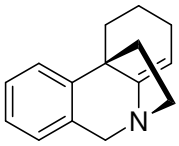
Around the world, the Amaryllidaceae family has found its place in the garden as ornamentals.[1] However, a huge number of plants are traded for traditional medicines as well. Use of the bulbs and leaves as poultices and decoctions for treating sores and digestive disorders is widespread among Africans. However, in large dosages these can prove to be extremely poisonous. The Zulu people of South Africa also use rhizomes of clivias as protective charms. In Peru, the Inca people frequently depicted flowers of the Amaryllidaceae (Ismene, Pyolirion and Stenomesson) on ceremonial drinking vessels. In cool temperate climates, Narcissus (daffodils), Leucojum (snowflakes) and Galanthus (snowdrops) are among the most important spring-flowering bulbs in commerce. Elsewhere, in warm temperate and subtropical climates, species of Amaryllis, Clivia, Hippeastrum, Nerine, and Zephyranthes are the most popular choices for gardens and containers.

The plants of the Amaryllidaceae family have attracted considerable attention due to their content of alkaloids with interesting pharmacological activities.[2] Until recently, the Amaryllidaceae alkaloids have been classified structurally mainly into seven

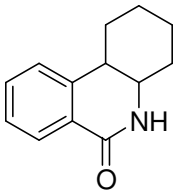
subgroups, namely lycorine (1H-pyrrolo[3,2,1-d,e] phenanthridine type), crinine (5,10b-ethanophenanthridine type), narciclasine (isocarbostyril type), galanthamine (6H-benzofuro[3a,3,2-e,f]-2- benzazepine type), tazettine (2-benzopyrano[3,4-c] indole type), lycorenine (2-benzopyrano[3,4-g]indole type) and montanine (5,11-methanomorphanthridine type).[3a-b] As a result of extensive phytochemical studies more than 500 different alkaloids have now been extracted from this family.[4]



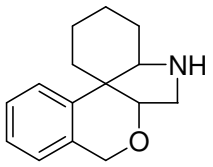
Lycorine



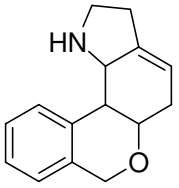
Crinine



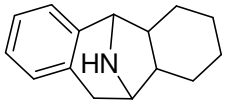
Narciclasine



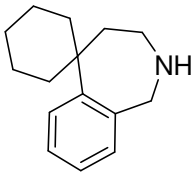
Tazettine



Lycorenine



Montanine

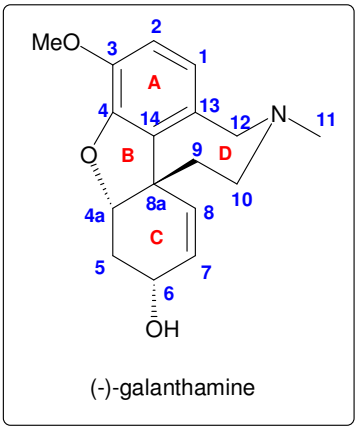


Galanthamine

Figure 3.01. Core structures of the alkaloids of the Amaryllidaceae family.

3.1.1 Isolation and Structure

Galanthamine, the most sought after among the Amaryllidaceae alkaloids, was first reported as a constituent of the Caucasian snowdrop (*Galanthus woronowii*) in 1952.[5] Its structure was confirmed by Uyeo and Kobayashi through degradation studies in 1957[6a-b] and, the absolute configuration was established as (-)-galanthamine by Barton and Kirby.[7] The extraction process provides about 10-100mg of galanthamine per kilogram of the raw plant material and the cost results in a price tag of $50,000 per kilogram of galanthamine.[8]



(-)-galanthamine

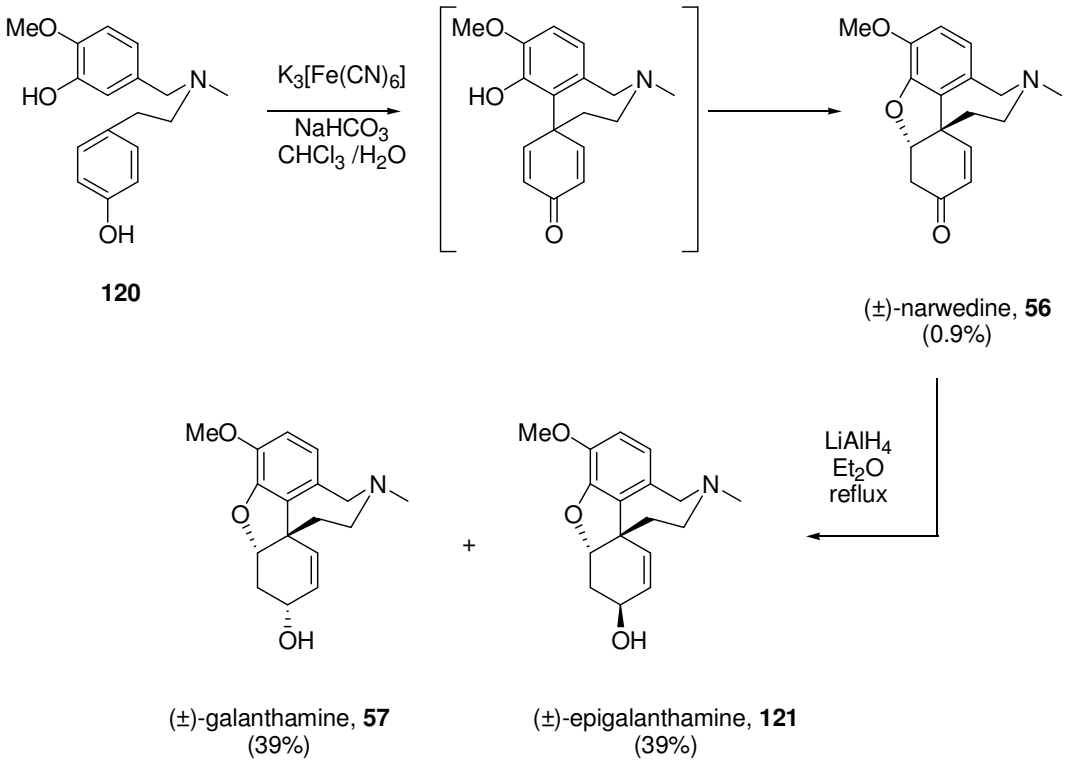
Figure 3.02 Structure of (-)-Galanthamine, **57**.

3.1.2 Pharmacology

Alzheimer 's disease (AD) is an incurable, degenerative, terminal disease which is one of the most common forms of dementia. Of the three hypotheses for the cause of the disease, the oldest, the cholinergic hypothesis states that the primary cause of AD is the reduction in the neurotransmitter acetylcholine (Ach). Acetylcholinesterase inhibitors are used to reduce the rate at which acetylcholine is broken down, and thus combat the loss of Ach. Galanthamine, is one such long acting, selective, reversible and competitive acetylcholinesterase inhibitor.[9a-c] The atomic resolution 3D structure of the complex of galanthamine and its target, acetylcholinesterase, was determined by X-ray crystallography in 1999.[10] However, there is no evidence that galanthamine alters the course of the underlying 'dementing' process. It is also used in the treatment of myasthenia gravis, an autoimmune disease which causes muscle weakness and fatigue.[11] For a long time, galanthamine has been used in Eastern Europe in the symptomatic treatment of poliomyelitis.[12] It is also used as an anti-curare agent,[13] and as a parasympathomimetic drug.[14] It is the most recently approved AchE inhibitor in Europe and US for the treatment of mild-to-moderate Alzheimer's disease.[15] Presently, it is marketed under the commercial name Razadyne™ (formerly Reminyl®).[16]

3.1.3 Previous syntheses

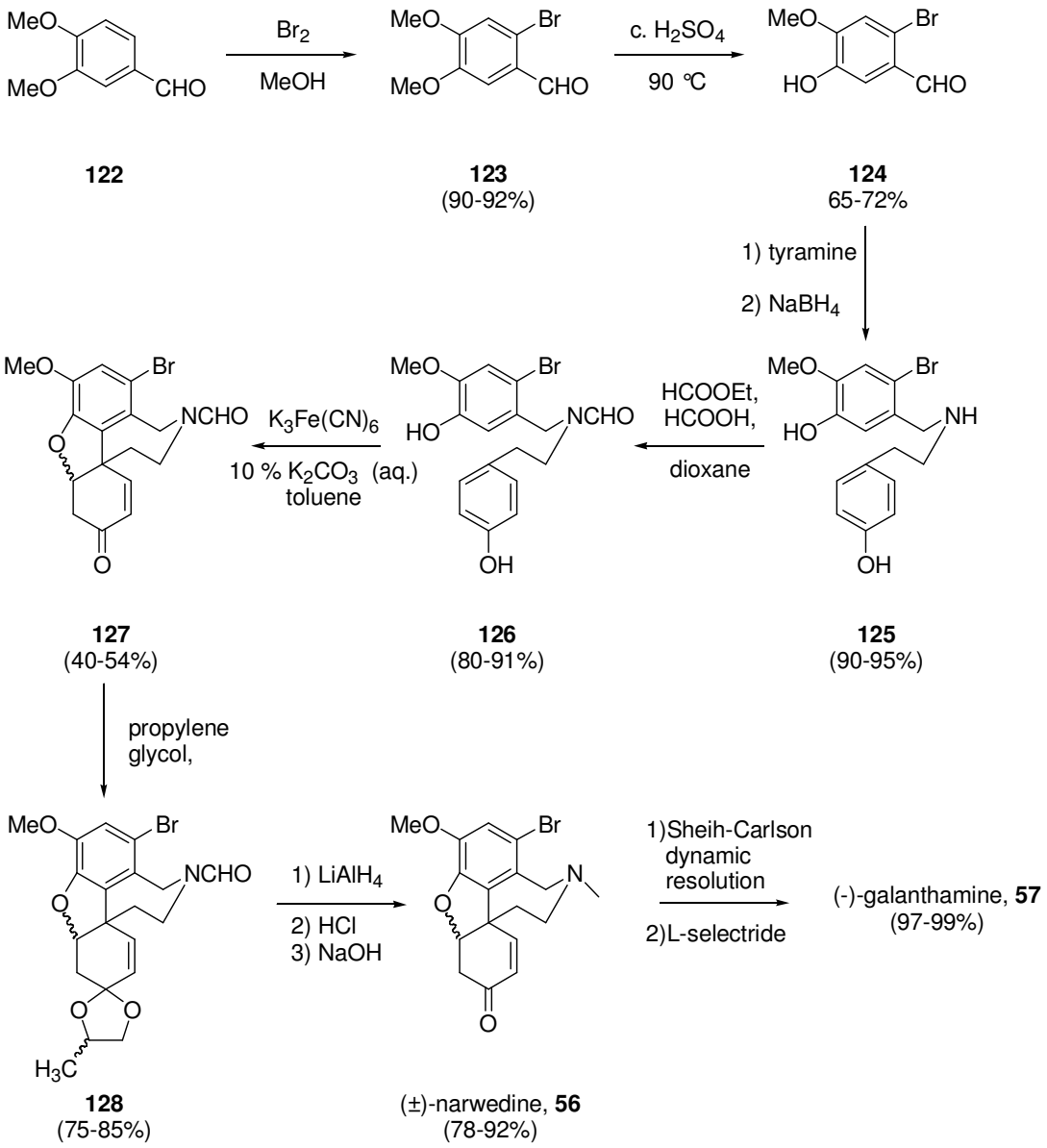
The first total synthesis of galanthamine was reported by Barton and Kirby in 1960 by the oxidative coupling in 4'-*O*-*N*-dimethylnorbelladine **120**, thus validating their proposed biosynthetic model, Scheme 3.01.[17]



Scheme 3.01. Barton and Kirby's biomimetic synthesis of (±)-galanthamine.

Subsequently, the synthesis of galanthamine has been improved upon by various research groups. The primary disconnections are similar to the strategies employed for the synthesis of morphine (discussed in Chapter 1), namely, the phenolic oxidative coupling[18a-m] and metal-catalyzed oxidative coupling[19a-c] of the A and C rings. There are also some other unique methods exclusively aimed at the synthesis of galanthamine.[20a-j]

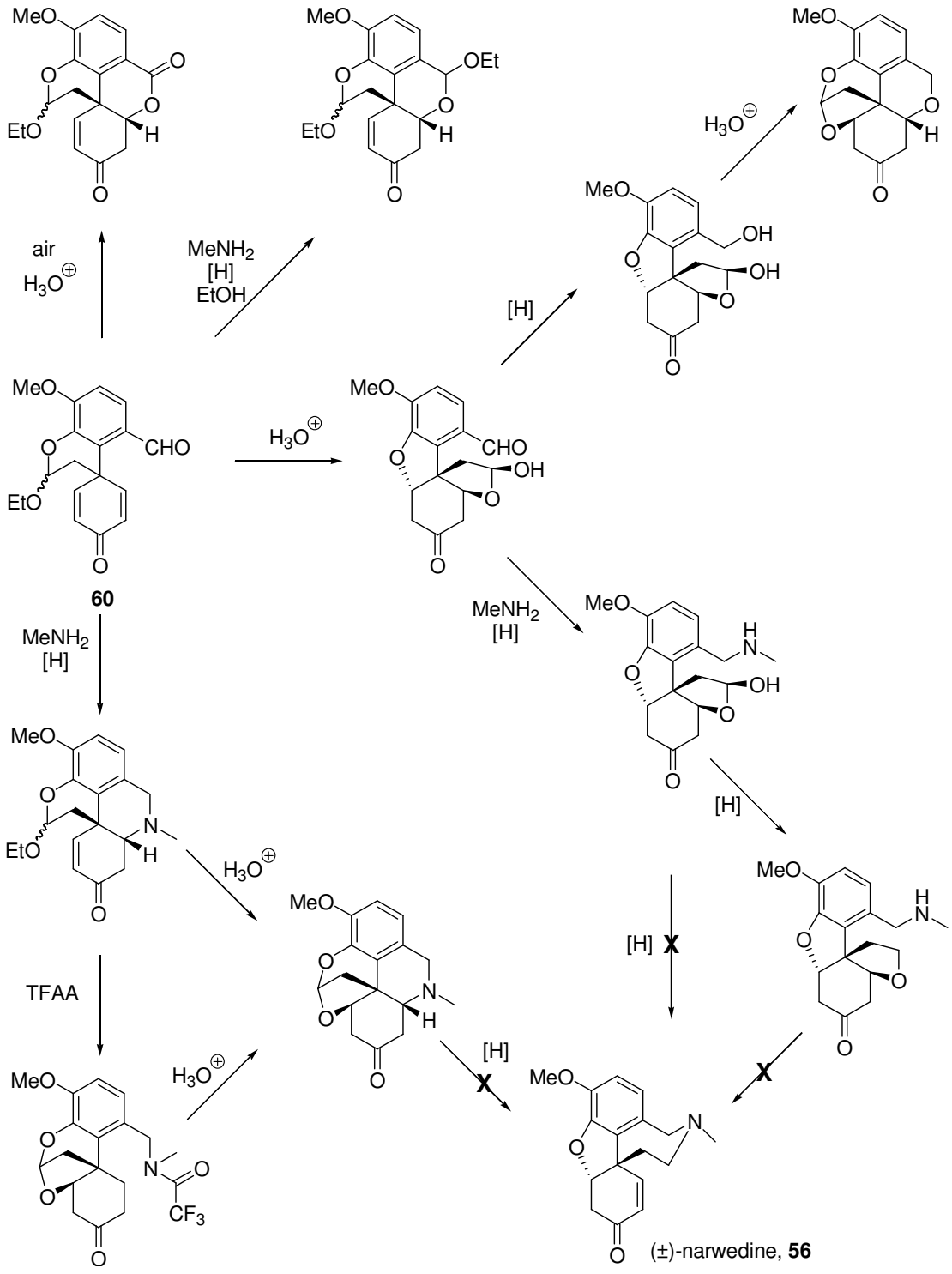
Currently, commercial supplies of the molecule are available from Sanochemia AG using the Fröhlich-Jordis route, Scheme 3.02.[21] The key phenolic oxidative coupling step using $K_3Fe(CN)_6$ proceeds in a modest 40-54% yield. This process route utilizes the Carlson-Shieh dynamic resolution procedure to convert (±)-narwedine using (+)-galanthamine to (-)-narwedine in the penultimate step.[22] The final step involves the reduction of (-)-narwedine using L-selectride to provide (-)-galanthamine in 99% yield. The overall yield for the nine steps synthesis is 12%.



Scheme 3.02. Sanochemia AG process route to (-)-galanthamine.

3.1.4 Previous work in the Magnus group

Previous studies in the Magnus group on the synthesis of (-)-galanthamine had envisioned the synthesis and double reductive amination of the dienone **60** with methylamine to provide (±)-narwedine, the precursor to (-)-galanthamine. This idea was initially pursued by Dr. Benjamin Fauber, then a graduate student in the lab and subsequently by a post-doctoral researcher Dr. Kimberley Seibert. However, various conditions and strategies at utilizing the dienone had not provided a scalable and reproducible synthesis of narwedine. A summary of this work is depicted in Scheme 3.03.



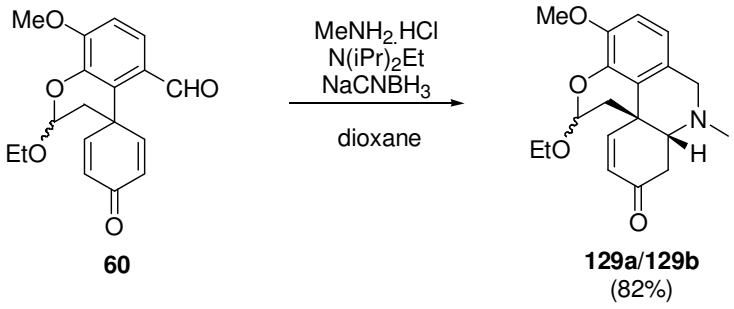
Scheme 3.03. Previous work in the Magnus group towards the synthesis of narwedine.

3.3 RESULTS AND DISCUSSION

In all of the previous attempts at the double reductive amination, the hydrolysis of the acetal, followed by the reductive amination was always attempted as a two step process. Having established in the morphine work (Chapter 1) that the hydrolysis-reductive amination could be performed sequentially in one step and, that the isolation of the imine was unnecessary, we envisioned using a similar approach in the construction of the seven-membered ring of narwedine from the dienone **60**.

Our prior experience in these reductive aminations had shown us that the use of methylamine as a solution in THF and other organic solvents for reductive aminations suffered from inconsistent results. Moreover, a bottle of methylamine (in solution) once opened, did not have a good shelf-life and could not be stored for more than 2-3 days. Older bottles would not only fail to aminate, but in fact, lead to complete decomposition of the reaction mixture. Owing to this, we decided to explore conditions in which the methyl amine could be liberated *in situ* within the reaction medium.

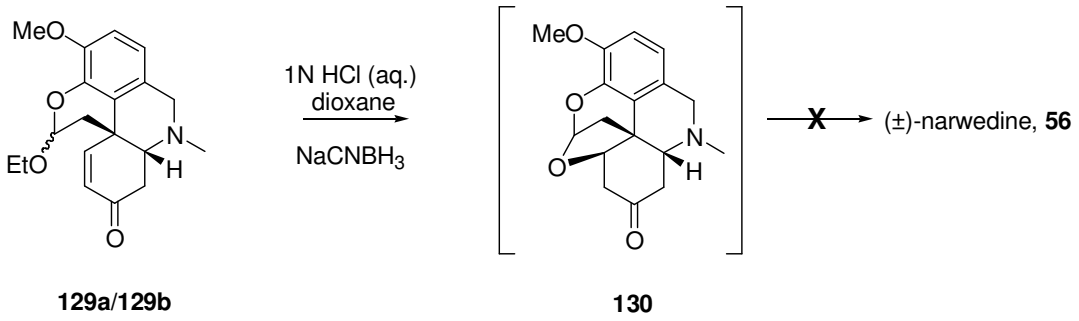
When a solution of the dienone **60** in dioxane was treated with methylamine hydrochloride and diisopropylethylamine followed by $NaCNBH_3$, complete conversion to the tricyclic amine **117** was obtained in 82% yield, Scheme 3.04.



60 **129a/129b** (82%)

Scheme 3.04. Synthesis of the tricyclic amine **129a/129b**.

When the amine **129a/129b** was subjected to hydrolysis under acidic conditions (1N HCl), followed by addition of $NaCNBH_3$, the major product of the reaction was the hydrolyzed acetal product **130**, Scheme 3.05. This product failed to reductively aminate even at temperatures in excess of 120 °C.

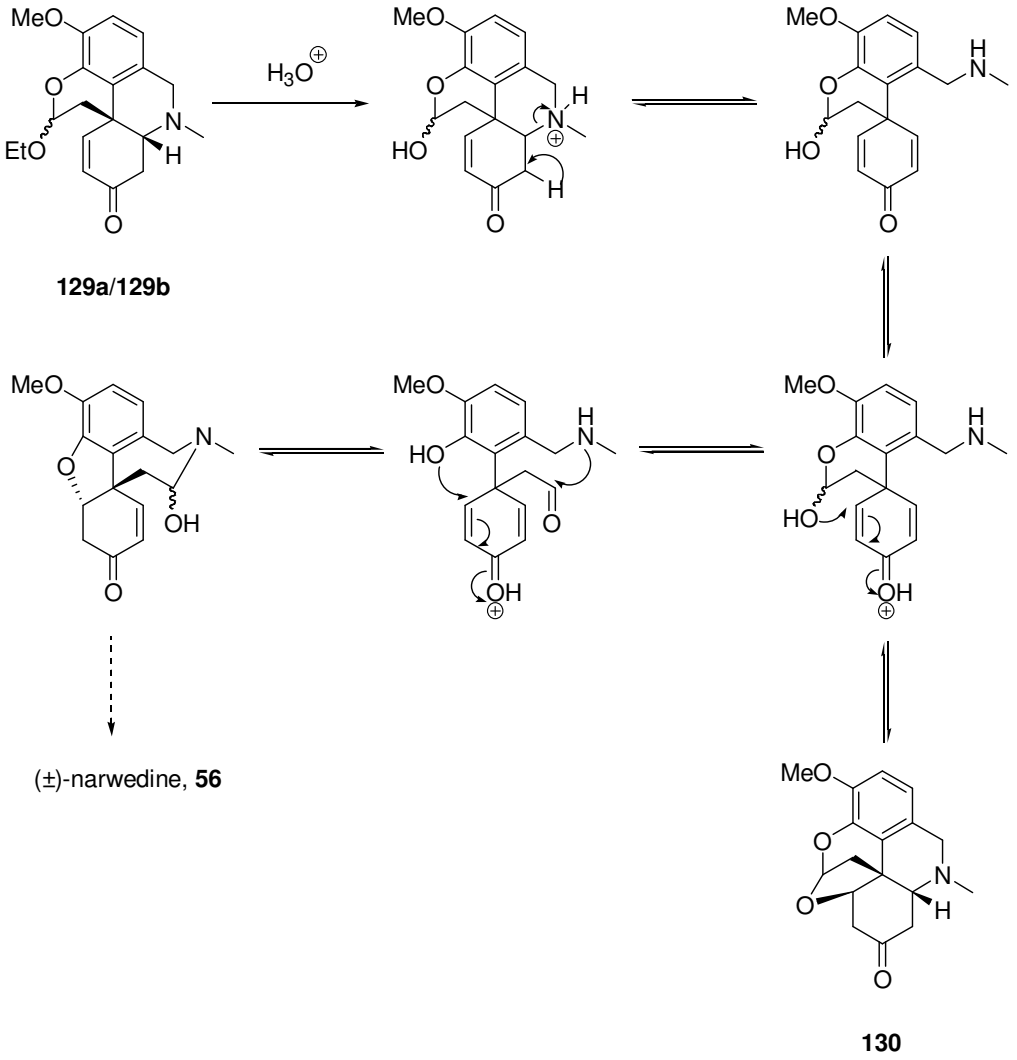


129a/129b **130**

Scheme 3.05. Hydrolysis of the tricyclic amine under reductive conditions

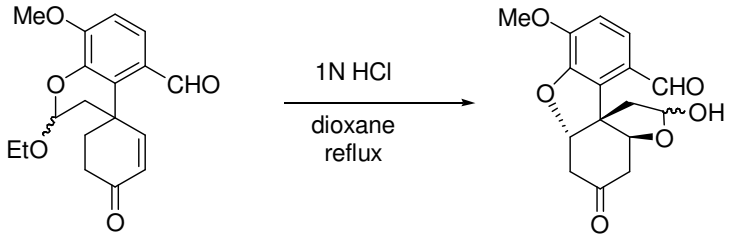
In order to avoid the hydrolysis product **130**, the acetal cleavage was performed in the presence of in 10% HCl in ethanol. However, the reductive amination to narwedine did not occur and the ^{1}H-NMR of the product showed the presence of several signals corresponding to the ethoxy group indicating that the saturated ketone may have formed the diethylketal under these conditions.

The failure of the one-step hydrolysis reductive amination protocol in this system can be attributed to the large energy barrier required to form the seven-membered D-ring from an existing six-membered tertiary amine. When the reductive amination fails, the competing 1,4 addition of the intermediate hemi-acetal results in the closure to the compound **118**, Scheme 3.06.



Scheme 3.06. Mechanistic pathway leading to (±)-narwedine.

It was clear that the competing conjugate addition pathway was to be avoided. One possible method was prior formation of the furan ring. This was achieved by the hydrolysis of the dienone **60** to the lactol **131** using aqueous hydrochloric acid in refluxing dioxane, in 93% yield, Scheme 3.07. The molecule has no available enone for the impeding conjugate addition of the amine, during the proposed amination reaction that followed.

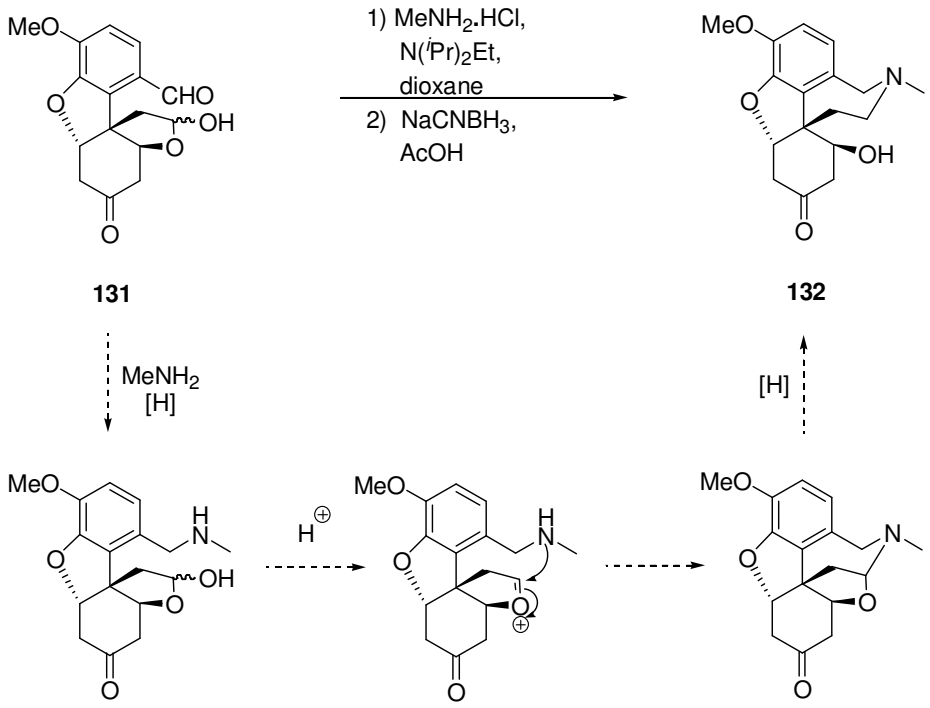


60 **131** (93%)

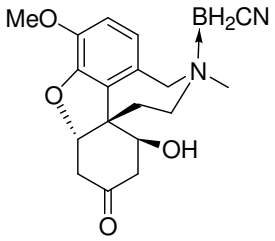
Scheme 3.07. Hydrolysis of the dienone

Treatment of the lactol with methylamine hydrochloride and *N*,*N*-diisopropylethylamine followed by treatment with $NaCNBH_3$ in acetic acid resulted in complete conversion to what was initially speculated to be the β-hydroxy ketone **132**, Scheme 3.08. The ^{1}H-NMR of the product showed the AB doublet of the benzylic protons and the proton at C4a (furan) that is a characteristic feature in the spectrum of narwedine. However, the enone signals were absent. We reasoned that that product was most likely the result of a stepwise amination, first with the benzaldehyde and subsequently with the oxonium ion generated from the lactol. Prominent signals in the IR

spectrum included the 1718 cm^{-1} of the saturated ketone and an unexpected doublet at 2200 cm^{-1} and singlet at 2414 cm^{-1}. X-ray analysis of the compound explained this unusual pattern by indicating the presence of a BH_2CN moiety on the tertiary nitrogen *via* a dative bond, Figure 3.04.



Scheme 3.08. Reductive amination of the lactol.



132a

Figure 3.03 Observed product of reductive amination.

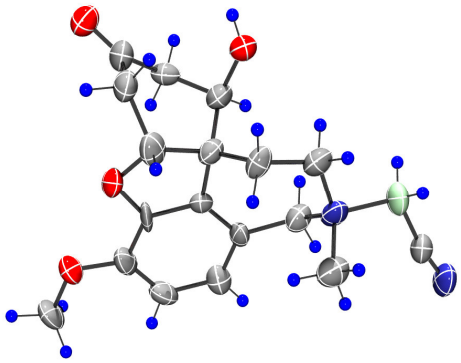
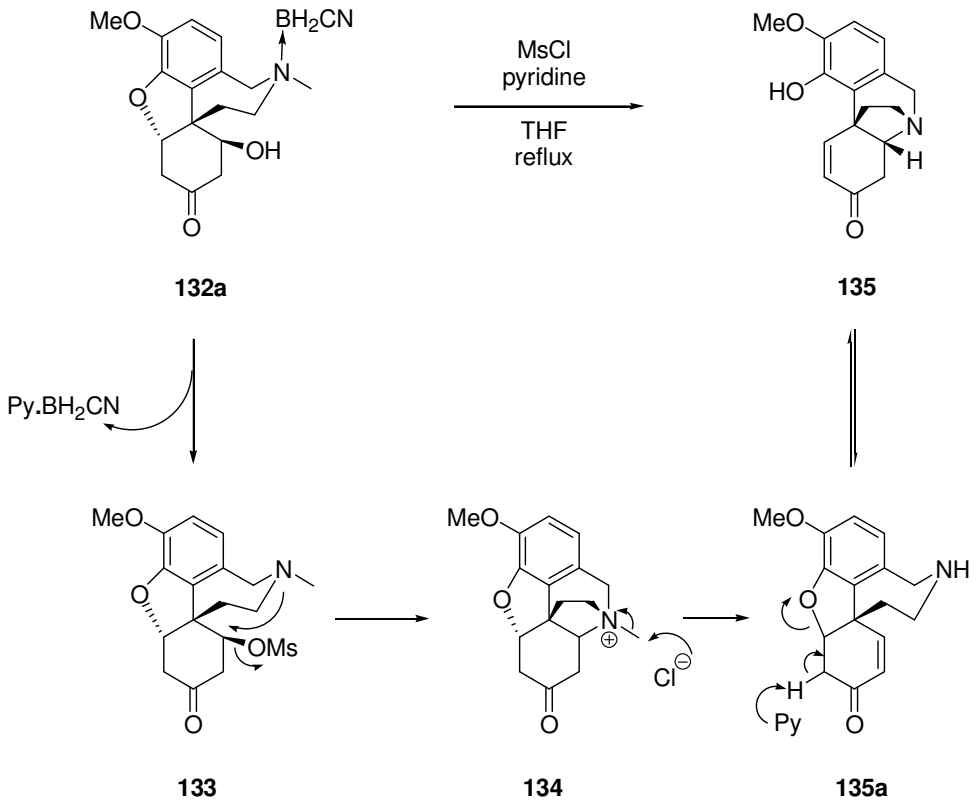


Figure 3.04. ORTEP representation of the borane adduct **132a**.

When the borane adduct **132a** was heated with mesyl chloride and pyridine, complete conversion to a less polar compound (TLC) occurred. This was speculated as being the mesylate of the β-hydroxyketone and was expected to readily eliminate to narwedine. When the resulting solution was heated with additional triethylamine, two products were observed by TLC; one having a similar R_f to narwedine and the other, more polar. Isolation of the individual products by preparative TLC and characterization by ^{1}H-NMR revealed that the N-methyl signal was conspicuously absent in the product.

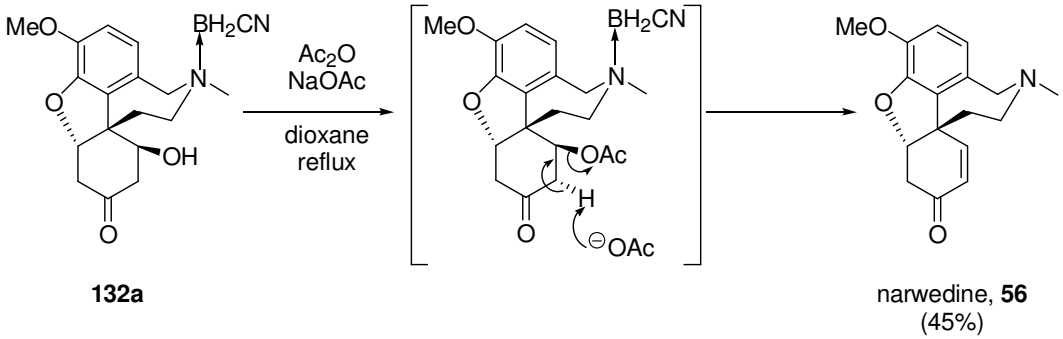
When a TLC analysis of the two separated compounds was performed, it was observed that each of the compounds was again a mixture of the two separated ones. Based on the spectral evidence, the compounds can be assigned the structures **135** and **135a**. The two products are believed to be an equilibrating mixture of the free secondary amine and the free phenol.

This equilibrating mixture has been previously observed by Jordis et. al. in their work related to the demethylation of narwedine.[23] Compound **135a** is in fact *N*-demethylated narwedine. Based on the mechanistic evidence presented in the citation, a rationale for the demethylation observed in this system is presented in Scheme 3.09.



Scheme 3.09. Demethylation product.

In order to prevent chloride assisted demethylation, observed during the mesylate elimination, the conversion of the β-hydroxy ketone to the enone was carried out *via* acetylation-elimination, Scheme 3.10. When the borane adduct **132a** was treated with a mixture of acetic anhydride and sodium acetate and heated at reflux in dioxane, complete conversion to narwedine (**56**) was observed. It is reasonable to assume that in the absence of a decomplexing agent such as pyridine, the nitrogen is still bound to the boron and hence unable to engage in the intramolecular S_N2 reaction observed in the intermediate **133**. Thus, the acetate intermediate eliminates under these conditions to eventually produce narwedine.



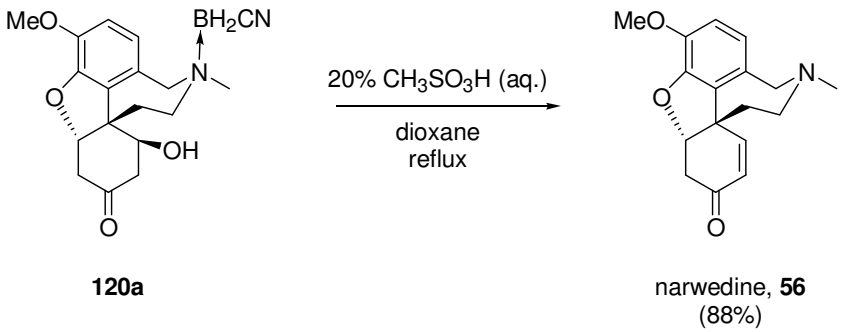
132a

narwedine, **56**
(45%)

Scheme 3.10. Elimination *via* acetylation.

A convenient method to disable neighboring group participation by the tertiary nitrogen, would be to perform the reaction under strongly acidic conditions which would lead to protonation of the nitrogen and render it non-nucleophilic. However, treatment of the hydroxy compound **132a** under various acidic conditions (aq. H_2SO_4, acetic acid, etc.) did not produce narwedine. Treatment of the compound **132a** under basic conditions (aq. sodium hydroxide) resulted in complete decomposition of the material.

When a solution of the compound **132a** in dioxane was treated with an aqueous solution of methanesulfonic acid (1M) and heated for several hours, complete conversion to a product identical in R_f to an authentic sample of narwedine was observed by TLC. Further spectroscopic data confirmed that the product was indeed narwedine.



120a

narwedine, **56**
(88%)

Scheme 3.11. Acid catalyzed elimination to (±)-narwedine.

Subsequent optimizations established that recrystallized methylamine hydrochloride provided the best yields of the β-hydroxy ketone **132a**. The crude product can be subjected to the dehydration conditions without purification. The dehydration was performed under refluxing dioxane with 20% methanesulfonic acid (aq.), Scheme 3.11. Complete conversion to narwedine was obtained and the overall yield for the three steps from the dienone **60** to narwedine is 67%.

The dynamic resolution of racemic narwedine to (-)-narwedine and the subsequent reduction to (-)-galanthamine has been well established and proceeds in 97% yield. Thus, the aforementioned synthesis of racemic narwedine constitutes a formal synthesis of (-)-galanthamine. The overall yield of the six step procedure, beginning with 2-bromoisovanillin, is 63% which is five times the yield of Sanochemia AG's commercial synthesis of (-)-galanthamine.

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CHAPTER 4: EXPERIMENTAL SECTION

4.0 GENERAL INFORMATION

Melting points were taken on a Thomas-Hoover capillary tube apparatus, and are uncorrected. Infrared spectra were recorded on a Thermo-Nicolet Avatar 360 FT-IR spectrophotometer, with the sample neat on KBr plates, unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz DirectDrive NMR at 400 MHz and General Electric QE-300 spectrometer at 300 MHz, in the indicated solvent, and are reported in ppm relative to tetramethylsilane, or referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E, or a Finnigan TSQ70 mass spectrometer.

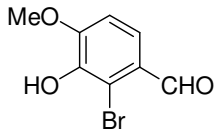
Routine monitoring of reactions was performed using Merck 60 F254 glass-backed silica gel TLC plates. Flash column chromatography was performed using EMD silica gel (particle size 0.040-0.063 μm). Solvents and commercial reagents were purified in accordance with Perrin and Armarego[1] or used without further purification. All reactions were conducted under an argon atmosphere, and solvents were degassed only when specified.

The determination of enantiomeric excess was performed using High performance liquid chromatography (HPLC) on a Waters 515 Binary HPLC pump fitted with a PDA detector (model # 2996) using a Chiralcel® OD-H column (4.6mm x 250mm) manufactured by Daicel Chemical Industries, LTD. The concentration of the analyte was approximately 1.0 mg mL^{-1} and the injection volume was 25 μL. The eluant used was a 3: 7 mixture of isopropyl alcohol and hexanes with a flow rate of 0.8 mL min^{-1}. Optical

rotations were performed using an Atago POLAX-2L optical resolution polarimeter with a 1.0 mL x 100 mm Atago glass observation tube at the specified temperature (°C), wavelength (nm), and concentration (g/100 mL).

4.1 EXPERIMENTAL CONDITIONS AND COMPOUND DATA FOR CHAPTER 1.

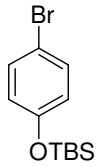
2-Bromo-3-hydroxy-4-methoxy-benzaldehyde 73.[2]



To a stirred suspension of isovanillin **72** (10 g, 66 mmol), powdered anhydrous sodium acetate (10.82 g, 0.132 mol) and iron powder (0.3 g, 5.4 mmol) in glacial acetic acid (60 mL) under argon, was added drop-wise over 15 min a solution of Br_2 (3.7 mL, 0.0726 mol) in acetic acid (12.5 mL). The reaction temperature rose during the course of addition, and the mixture became viscous. After all the starting material was consumed, as judged by TLC, the mixture was poured onto ice cold water, and the resulting precipitate filtered under vacuum. The precipitate was washed several times with cold water and air dried. Crystallization from boiling ethanol gave **73** (11.93 g, 79 % yield) as a grey powder.

R_f = 0.10 (1:5 EtOAc/hexanes). M.p. 196-200 °C. IR (thin film) 3215, 1662, 1588, 1561, 1491, 1273 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 10.27 (1H, s), 7.59 (1H, d, *J* = 9 Hz), 6.96 (1H, d, *J* = 9 Hz), 6.02 (1H, bs), 4.00 (3H, s). ^{13}C NMR (75MHz, $CDCl_3$) δ 56.58, 109.24, 112.84, 113.84, 122.74, 143.25, 151.65, 190.87. HRMS calcd. for $C_8H_8O_3Br$ (MH^+) 230.9657, found 230.9652.

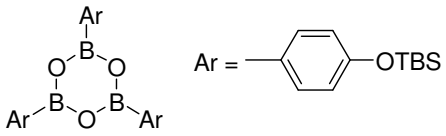
(4-Bromo-phenoxy)-*tert*-butyl-dimethylsilane 75.[3]



To a stirred solution of *p*-bromophenol (30 g, 0.1734 mol) in 1, 2-dichloroethane (300 mL) at 23 °C was added imidazole (29.45 g, 0.433 mol). After 15 min, *tert*-butyldimethylsilylchloride (28.75 g, 0.190 mol) was added, and the resulting solution heated at reflux for 3 h. The mixture was cooled to room temperature and poured onto saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 200 mL). The combined extracts were washed with brine (200mL), dried ($NaSO_4$), filtered and evaporated *in vacuo*. The crude product was distilled via short-path distillation (0.5 mm Hg, 130 °C) to give (4-bromo-phenoxy)-*tert*-butyl-dimethylsilane (49.6 g, 99.5% yield) as a colorless oil.

R_f = 0.80 (1:3 EtOAc/hexanes). IR (thin film) 3390, 2951, 2928, 1584, 1479, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 9 Hz), 6.74 (1H, d, *J* = 9 Hz), 1.00 (12H, s), 0.21 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.76, 132.22, 121.83, 113.55, 25.58, 18.12, -4.54. HRMS calcd. for $C_{12}H_{20}BrOSi$ (MH^+) 287.0461, found 287.0463.

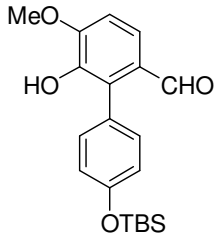
2,4,6-Tris-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-cyclotriboroxane 76.[4]



To a solution of (4-bromo-phenoxy)-*tert*-butyl-dimethylsilane **75** (10 g, 35 mmol) in THF (25 mL) at -78 °C was added drop-wise *n*-butyllithium (2.4 M in hexanes, 17.5 mL, 42 mmol) resulting in a yellow colored solution. After stirring the mixture for 30 min, freshly distilled triisopropoxyborate (24.2 mL, 105 mmol) was added drop-wise to the above solution, and the mixture was stirred overnight and allowed to warm to room temperature. The mixture was poured onto 10% aqueous $KHSO_4$ (50 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude white solid was dried by azeotroping in toluene (3 x 20 mL), and recrystallized from hexanes/EtOAc to give needle shaped crystals of **76** (6.9 g, 84.5 % yield).

R_f = 0.12 (1:5 EtOAc/hexanes). M.p.118-120 °C. IR (thin film) 2955, 2928, 2854, 1592 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8 Hz), 6.97 (2H, d, *J* = 8 Hz), 1.03 (9H, s), 0.27 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 137.4, 119.8, 25.7, 18.3, -4.3. HRMS calcd. for $C_{36}H_{58}B_3O_6Si_3$ (MH^+) 703.3820, found 703.3826.

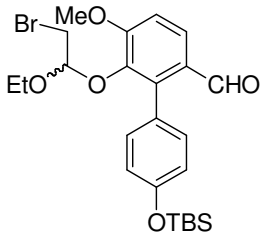
4'-(*tert*-Butyl-dimethyl-silanyloxy)-6-hydroxy-5-methoxy-biphenyl-2-carbaldehyde 77.



To a degassed (30 min) mixture of 1,4-dioxane (22.5 mL) and water (7.5 mL) was added powdered K_2CO_3 (2.48 g, 18 mmol), **72** (1.53 g, 6.6 mmol), **76** (1.5 g, 6 mmol), 2,6-di-*tert*-butyl-4 methylphenol (BHT) (spatula), and tricyclohexylphosphine (67 mg, 0.24 mmol). The mixture stirred for 15 min at 23 °C and $[Pd_2(dba)_3]$ (0.114 g, 0.12 mmol) was added, and then heated at reflux for 1 h until all starting material was consumed, as judged by TLC. The resulting dark colored solution was poured onto saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow solid. Purification by flash column chromatography (SiO_2, 15% EtOAc/hexanes) gave **77** (2.1 g, 87.9% yield) as a pale yellow solid.

R_f = 0.20 (1:5 EtOAc/hexanes). M.p. 103-106 °C. IR (thin film) 3401, 2930, 2857, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (1H, s), 7.65 (1H, d, *J* = 9 Hz), 7.24 (1H, d, *J* = 9 Hz), 6.98 (1H, d, *J* = 9 Hz), 6.95 (1H, d, *J* = 9 Hz), 5.67 (1H , bs), 4.02 (3H, s), 1.02 (9H, s), 0.26 (6H, s). ^{13}C NMR (75MHz, $CDCl_3$) δ 191.6, 155.7, 150.8, 142.7, 132.0, 131.5, 128.4, 120.5, 119.8, 109.6, 56.2, 25.6, 18.2, -4.4. HRMS calcd. for $C_{20}H_{27}O_4Si$ (MH^+) 359.1679, found 359.1675.

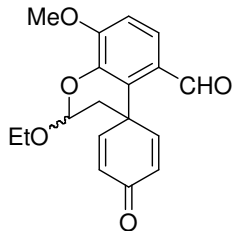
6-(2-Bromo-1-ethoxy-ethoxy)-4'-(tert-butyl-dimethyl-silanyloxy)-5-methoxy-biphenyl-2-carbaldehyde 79.



To a solution of Br_2 (0.397 mL, 7.74 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added drop-wise ethyl vinyl ether (0.92 mL, 9.68 mmol) until the solution turned colorless. The mixture was stirred for 15 min and diisopropylethylamine (2.71 mL, 15.48 mmol) was added followed by a drop-wise addition of a solution of **77** (1.5 g, 3.87 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 12 h under argon to give an orange-red solution. After complete consumption of staring material, as judged by TLC, the mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo* to give an orange-red oil. Purification by flash column chromatography (SiO_2, 10% EtOAc/Hexanes) gave **79** (1.92 g, 92 % yield) as a colorless syrupy liquid. (1.92 g, 92% yield).

R_f = 0.42 (1:5 EtOAc/hexanes). IR (thin film) 2956, 2930, 2857, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (1H, s), 7.85 (1H, d, *J* = 9 Hz), 7.25-7.18 (2H, m), 7.03(1H, d, *J* = 9 Hz) , 6.93 (2H, d, *J* = 9 Hz), 5.01(1H, dd, *J's* = 7, 4 Hz), 3.98 (3H, s), 3.56 (1H, m), 3.31 (1H, m), 3.09 (2H,m), 1.05 (2H, t, 7 Hz), 1.01 (9H, s), 0.24 (6H,s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 157.02, 155.8, 141.7, 140.6, 132.5, 128.5, 125.2, 119.7, 111.0, 103.7, 64.5, 55.9, 31.8, 25.6, 18.2, 14.9, -4.4. HRMS calcd. for $C_{24}H_{34}O_5SiBr$ (MH^+) 509.1359, found 509.1356.

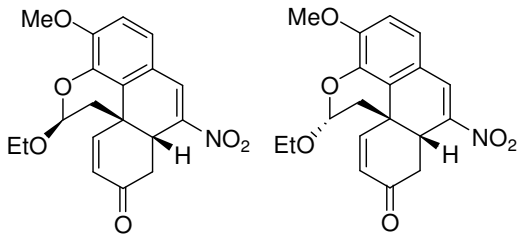
Cross-conjugated cyclohexadienone 60



A flame-dried mixture of CsF (0.22 g, 1.44 mol) and Na_2SO_4 (0.68 g, 4.8 mmol) was added to a solution of **79** (0.26 g, 0.48 mmol) in DMF (3.7 mL, stored over 4Å molecular sieves) and the reaction mixture was heated at 130 °C for 1.5 h. After completion of the reaction, as judged by TLC, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) and extracted with EtOAc (4 x 20 mL). The combined extracts were successively washed with water (3 x 25 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown syrup. Purification by flash chromatography (SiO_2, 30% EtOAc/hexanes) gave compound **60** (0.137 g, 95.5% yield) as thick orange oil which solidified upon standing to an orange solid.

R_f = 0.23 (1:1 EtOAc/hexanes). M.p. 74-80 °C. IR (thin film) 2983, 2932, 2889, 1684, 1663, 1586 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.75 (1H, dd, *J's* = 10, 3 Hz), 7.64 (1H, d, *J* = 9 Hz), 7.04 (1H, *J's* = 10, 3 Hz), 6.98 (1H, d, *J* = 9 Hz), 6.38 (1H, dd, *J*'s = 8, 2 Hz), 6.36 (1H, dd, *J's* = 8, 2 Hz), 5.15 (1H, t, *J* = 2 Hz), 4.00 (s, 3H), 3.96 (1H, m), 3.70 (1H, m), 2.40 (1H, dd, *J's* = 14, 2 Hz), 2.01 (1H, dd, *J's* = 14, 2 Hz), 1.22 (3H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 184.4, 155.8, 155.5, 154.5, 140.1, 128.7, 126.0, 123.3, 122.8, 110.7, 94.8, 64.7, 56.2, 40.2, 39.8, 15.0. HRMS calcd. for $C_{18}H_{19}O_5$ (MH^+) 315.1232, found 315.1231.

6-Ethoxy-8-methoxy-12-nitro-1,5,6,12a-tetrahydro-naphtho[8a,1,2-de]chromen-2-one 12/12a.



80a **80b**

A mixture of the dienone **60** (1.0 g, 3.18 mmol), NH_4OAc (0.98 g, 12.7 mmol), and nitromethane (1.01 mL, 19.08 mmol) in acetic acid (15 mL) was heated at reflux for 2 h. After completion of the reaction, as judged by TLC, the solvent was evaporated *in vacuo* and the residue was washed with water (40 mL) and extracted with diethylether (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown solid. Purification by flash chromatography (SiO_2, 20% EtOAc/hexanes) gave bright yellow crystals of the two diastereomers **80a** and **80b** (0.72 g, 63% yield) in approximately 1:1 ratio.

Data for **80a**. R_f = 0.45 (1:1 EtOAc/Hexanes). M.p. 161-164 °C. IR (thin film) 2974, 2926, 2853, 1684, 1570 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 2 Hz), 7.00 (1H, d, *J* = 9 Hz), 6.90 (1H, d, *J* = 9 Hz), 6.75 (1H, dd, *J's* = 10, 1.5 Hz), 5.92 (1H, d, *J* = 10 Hz), 5.59 (1H, d, *J* = 3 Hz), 3.95 (1H, m), 3.96 (3H, s), 3.70 (1H, m), 3.45 (1H, dd, *J's* = 4, 2 Hz), 3.27 (1H, dd, *J* = 9, 1.5 Hz), 2.88 (1H, dd, *J* = 18, 5 Hz), 2.70 (1H, dd, *J's* = 13, 1.5 Hz), 2.33 (1H, dd, *J's* = 13, 3 Hz), 1.20 (3H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 152.3, 147.4, 140.4, 132.2, 126.9, 123.9, 121.3, 110.9, 96.2, 68.1, 64.6, 56.1, 43.1, 37.2, 36.2, 34.4, 29.64, 15.1. Both the structures of **80a** and **80b** were elucidated by X-ray.

Data for **80b**. R_f = 0.47 (1:1 EtOAc/hexanes). M.p. 165-170 °C. IR (thin film) 2920, 2842, 1685, 1565 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2 Hz), 6.96 (1H, d, *J* = 8 Hz), 6.86 (1H, d, *J* = 8 Hz), 6.48 (1H, dd, *J's* = 10, 2 Hz), 5.98 (1H, d, *J* = 10 Hz), 5.38 (1H, dd, *J*'s = 9, 3 Hz), 4.16 (1H, m), 3.92 (3H, s), 3.74 (1H, m), 3.50 (1H, m), 3.28 (1H, dd, *J's* = 6, 2 Hz), 2.89 (1H, dd, *J's* = 18, 5 Hz), 2.66 (1H, dd, *J*'s = 13, 3 Hz), 2.27 (1H, dd, *J*'s = 13, 9 Hz), 1.29 (3H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 150.0, 146.9, 141.4, 132.2, 128.7, 123.9, 121.3, 111.3, 97.7, 65.3, 56.1, 42.1, 39.1, 38.8, 34.2, 15.1. HRMS calcd. for $C_{19}H_{20}NO_6$ (MH^+) 358.1291, found 358.1290.

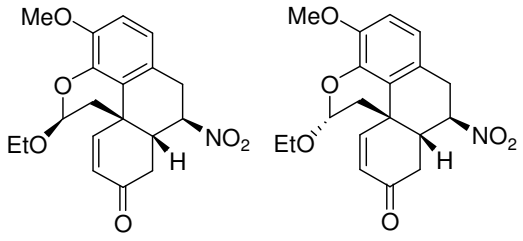
Alternative Procedure

To the dienone **6** (5.0 g, 15.93 mM) in nitromethane (50 mL), was added NH_4OAc (0.5 g) and acetic acid (5 mL) and the solution was heated at reflux for 2.5 h. When **6** had been consumed, as judged by TLC, the mixture was poured into brine (50 mL) and the layers separated. The aqueous layer was successively washed with ether (2 x 40 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give (5.5 g, 97 % yield) of **80a/80b** as a mixture of two diastereomers in a 1:1 ratio. NMR analysis indicated that the crude mixture was pure enough to be carried forward without purification.

Procedure for the synthesis of the nitroalkenes 80a/80b from the chiral nitroalcohols 114a/114b.

To a solution of the nitroalcohol **114a** (20 mg, 0.54 mM), in THF (2mL) was added triethylamine (0.3 mL) followed by methanesulfonyl chloride (0.06 mL, 0.80 mM) and the solution was heated at reflux until complete conversion to the nitroalkene **80a** was observed as judged by TLC. The reaction mixture was poured into saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a bright yellow solid (16 mg, 85% yield). For the purpose of HPLC analysis, the compound was recrystallized from hot toluene to give the title compound as bright yellow needle shaped crystals.

6-Ethoxy-8-methoxy-12-nitro-1,5,6,11,12,12a-hexahydro-naphtho[8a,1,2-de]chromen-2-one 81a/81b.



81a **81b**

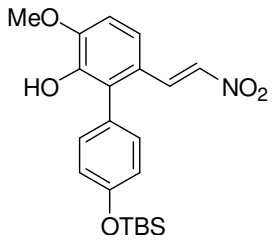
To a solution of the nitroalkenes **81a/81b** (127 mg, 0.36 mmol) in THF (3.5 mL) and acetic acid (1.5 mL) was added $NaBH_3CN$ (23.5 mg, 0.37 mmol) in small portions, and the resulting solution was stirred at for 4 h until all the starting material was consumed as judged by TLC. The mixture was poured into aqueous NH_4Cl (5 ml) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow solid. Purification by flash column chromatography (SiO_2, 30 % EtOAc/hexanes) gave **13** and **13a** as white solids (112 mg, 88% yield)..

Data for **81a**. R_f = 0.55 (1:1 EtOAc/Hexanes). M.p. 201 °C. IR (thin film) 2975, 2932, 1685, 1551 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (2H, m), 6.06 (1H, d, *J* = 10 Hz), 5.50 (1H, dd, *J's* = 8, 6 Hz), 4.92 (1H, m), 4.10 (1H, m), 3.88 (3H, s), 3.67 (1H, m), 3.33 (2H, m), 2.86 (3H, m), 2.46 (1H, d, *J* = 18 Hz), 2.00 (1H, dd, *J's* = 13, 8 Hz), 0.26 (3H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 152.0, 148.6, 141.0, 128.5, 125.2, 122.2, 121.5, 112.5, 98.2, 83.8, 64.4, 56.2, 43.6, 42.4, 38.1, 35.9, 33.2, 29.6, 14.9; HRMS calcd. for $C_{19}H_{22}NO_6$ (MH^+) 360.1447, found 360.1443. Structures of **81a** and **81b** by X-ray.

Data for **81b**. R_f = 0.57 (1:1 EtOAc/Hexanes). M.p. 168 °C. IR (thin film) 2975, 2932, 1684, 1551 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 9 Hz), 6.82 (1H,

dd, *J*'s = 10, 4 Hz), 6.73 (1H, d, *J* = 9 Hz), 6.06 (1H, d, *J* = 10 Hz), 5.50 (1H, dd, *J's* = 8, 6 Hz), 4.92 (1H, m), 4.10 (1H, m), 3.88 (3H, s), 3.67 (1H, m), 3.33 (2H, m), 2.86 (3H, m), 2.46 (1H, d, *J* = 18 Hz), 2.00 (1H, dd, *J's* = 13, 8 Hz), 0.26 (3H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 152.0, 148.6, 141.0, 128.5, 125.2, 122.2, 121.5, 112.5, 98.2, 83.8, 64.4, 56.2, 43.6, 42.4, 38.1, 35.9, 33.2, 14.9. HRMS calcd. for $C_{19}H_{22}NO_6$ (MH^+) 360.1447, found 360.1443.

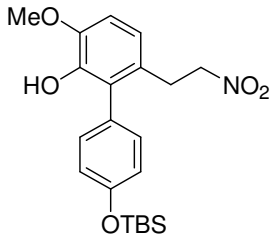
4'-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-6-(2-nitro-vinyl)-biphenyl-2-ol 84



To a solution of the biaryl compound (0.1g, 0.26 mmol) in nitromethane (2ml) was added NH_4OAc (0.015g, 0.19 mmol) and the solution was heated at reflux for 12 h. The solvent was evaporated under vacuum and the crude mixture was washed with water (15 ml) and extracted with EtOAc (3 x 15 ml) washed with washed with brine (20 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow solid. This was subjected to flash column chromatography (SiO_2, 20% EtOAc/Hexanes) to yield the title compound as a bright yellow solid (0.1g, 97% yield).

R_f 0.60 (1:1 EtOAc/Hexanes); M.p. 122-124°C IR (thin film) 3526, 2956, 2930, 2858, 1602, 1514, 1482, 1339, 1271, 1119, 912, 839, 804, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 14 Hz), 7.28 (1H, d, *J* = 14 Hz), 7.25 (1H, d, *J* = 8 Hz), 7.16 (2H, d, *J* = 8 Hz), 6.96 (2H, d, *J* = 8 Hz), 6.93 (1H, d, *J* = 8 Hz), 5.66 (1H, s), 4.00 (s, 3H), 1.02 (9H, s), 0.27 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 149.3, 143.4, 138.5, 135.9, 131.6, 130.1, 126.4, 122.7, 120.3, 120.2, 109.2, 56.2, 18.2, -4.3; HRMS calcd. for $C_{21}H_{28}NO_5Si$ [MH^+]: 402.1737, Found 402.1740.

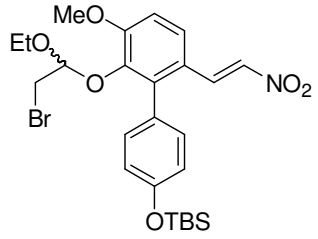
4'-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-6-(2-nitro-ethyl)-biphenyl-2-ol, 85.



$NaBH_4$ (0.2g, 3.44 mmol) was stirred in 10:1 THF/MeOH (15ml) for 30 mins. The resulting solution was added drop-wise to a solution of the nitroalkene (1.0g, 1.81 mmol) in a 10:1 mixture of THF/MeOH (35ml) cooled to -40 °C, until all starting material was fully consumed by TLC. The reaction mixture was warmed to -10 °C and quenched with a few drops of saturated NH_4Cl and 30 ml of water followed by extraction with EtOAc (3 x 25 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow liquid. This was subjected to flash column chromatography (SiO_2, % EtOAc/Hexanes) to yield the title compound as a colorless liquid (0.86g, 86% yield).

R_f 0.67 (1:1 EtOAc/Hexanes) M.p. 80-82°C; IR (thin film) 3507, 2956, 2930, 2858, 1553, 1514, 1484, 1263, 1168, 1121, 1030, 1012, 913, 840, 805, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8 Hz), 6.96 (2H, d, *J* = 8 Hz), 6.81 (1H, d, *J* = 8 Hz), 6.75 (1H, d, *J* = 8 Hz), 5.54 (1H,s), 4.23 (2H, t, J = 8 Hz), 3.91 (3H, s), 3.12 (2H, t, *J* = 8 Hz), 1.02 (9H, s), 0.26 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 146.0, 143.4, 131.0, 130.8, 127.8, 127.0, 120.5, 120.4, 109.8, 75.5, 56.0, 31.0, 31.1, 25.6, 25.6, 18.2, -4.4; HRMS calcd. for $C_{21}H_{29}NO_5Si$ [MH^+]: 403.1815, Found 403.1816.

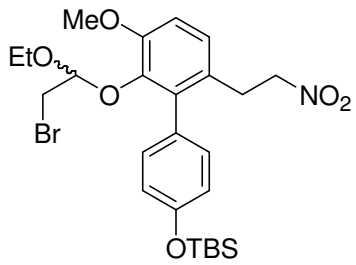
[2'-(2-Bromo-1-ethoxy-ethoxy)-3'-methoxy-6'-(2-nitro-vinyl)-biphenyl-4-yloxy]-tert-butyl-dimethyl-silane, 86



A solution of Br_2 (0.1ml, 2.0 mmol) in DCM (8ml) under argon, was cooled to 0 °C. To this, ethyl vinyl ether (0.24ml) was added drop-wise until the solution turned colorless. After 15 mins. of stirring, diisopropylethylamine (0.7 ml, 4.0 mmol) was added followed by a drop-wise addition of a solution of the biarylnitroalkene compound (0.4g, 1.0 mmol) in DCM (4ml). The reaction mixture was stirred for 12 h under argon. After complete consumption of staring material, checked by TLC, the reaction mixture was poured into saturated $NaHCO_3$ (20ml) and extracted with DCM (3 x 20ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an orange solid. This was subjected to flash column chromatography (SiO_2, % EtOAc/Hexanes) to yield the title compound as a bright yellow solid (0.44g, 80% yield).

R_f 0.29 (1:5 EtOAc/Hexanes); M.p. 113-115°C ; IR (thin film) 2930, 1589, 1512, 1476, 1340, 1263, 1126, 1011, 912, 839, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (1H, d, *J* = 14 Hz), 7.46 (1H, d, *J* = 8 Hz), 7.31 (1H, d, *J* = 14 Hz), 7.13 (2H, bs), 6.99 (2H, d, *J* = 8 Hz), 6.96 (1H, d, *J* = 8 Hz), 5.00 (1H, dd, J = 7, 4 Hz), 3.97 (3H, s), 3.57 (1H, m), 3.31(1H, m), 3.08 (2H,m), 1.05 (3H, t, *J* = 7 Hz), 1.02 (9H, s), 0.26 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 155.3, 142.7, 139.2, 138.1, 136.0, 132.0, 127.0, 124.8, 122.8, 120.1, 111.5, 103.7, 64.4, 55.9, 31.7, 25.7, 18.2, 14.9, -4.4; HRMS calcd. for $C_{25}H_{34}NO_6SiBr$ [MH^+]: 551.1339, Found 551.1335.

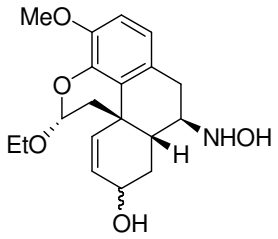
[2'-(2-Bromo-1-ethoxy-ethoxy)-3'-methoxy-6'-(2-nitro-ethyl)-biphenyl-4-yloxy]-tert-butyl-dimethyl-silane, 87.



$NaBH_4$ (0.2g, 3.44 mmol) was stirred in 10:1 THF/MeOH (15ml) for 30 mins. The resulting solution was added drop-wise to a solution of the nitroalkene (1.0g, 1.81 mmol) in a 10:1 mixture of THF/MeOH (35ml) cooled to -40 °C, until all starting material was fully consumed by TLC. The reaction mixture was warmed to -10 °C and quenched with a few drops of saturated NH_4Cl and 30 ml of water followed by extraction with EtOAc (3 x 25 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow liquid. This was subjected to flash column chromatography (SiO_2, % EtOAc/Hexanes) to yield the title compound as a colorless liquid (0.86g, 86% yield).

R_f 0.40 (1:5 EtOAc/Hexanes); IR (thin film) 2931, 2957, 1607, 1557, 1515,1481, 1435, 1262, 1169, 1124, 1012, 913, 841, 782, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, dd, *J* = 8, 2 Hz), 7.10 (1H, dd, *J* = 8, 2 Hz), 6.98 (1H, d, *J* = 9 Hz), 6.93 (2H, d, *J* = 8 Hz), 6.85 (1H, d, *J* = 9 Hz), 4.97 (1H, t, J = 6 Hz), 4.12 (2H, t, *J* = 7 Hz), 3.86 (3H, s), 3.56 (1H, m), 3.26 (1H, m), 3.24 (2H,m), 1.05 (3H, t, *J* = 7 Hz), 1.00 (9H, s), 0.24 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 151.9, 142.8, 136.8, 131.8, 130.9, 128.6, 127.0, 125.8, 120.2, 120.1, 111.3, 103.7, 75.3, 64.2, 55.9, 31.9, 31.1, 25.7, 25.6, 18.2, 14.9, -4.4; HRMS calcd. for $C_{25}H_{34}NO_6SiBr$ [MH^+]: 551.1339, Found 551.1335.

6-Ethoxy-12-hydroxyamino-8-methoxy-1,5,6,11,12,12a-hexahydro-2H-naphtho[8a,1,2-de]chromen-2-ol, 90b



90b

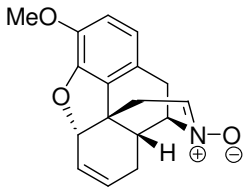
The aluminum amalgam required for the reaction was prepared as follows: 100 mg of aluminum foil was cleaned with hexanes and cut into thin strips. The strips were immersed into an aqueous solution (5ml) of $HgCl_2$ (1%) for 30 s, followed by water for 10 s and finally THF for 10 s.

To a solution of the nitroalkane **90a** 100mg (0.28 mM) in 9:1 THF/MeOH (10ml) was added freshly prepared aluminum amalgam (100mg). The suspension tuned gray after 20 min and complete consumption of starting material to product was observed, as judged by TLC. The slurry was filtered over Celite and washed several times with ether. The combined washings were washed with brine (10 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a foamy white solid (72 mg, 75% yield) which was used without purification for the subsequent step. The compound can be purified *via* flash column chromatography (SiO_2, 5% MeOH/$CHCl_3$) to give the title compound **90b** as a white foam (42 mg, 87%).

R_f = 0.54 (10% MeOH/$CHCl_3$). IR (thin film) 3355, 3276, 2972, 2931, 1611, 1580, 1498, 1440, 1276, 1230, 1129, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (1H, d, *J* = 8.4 Hz), 6.70 (1H, d, *J* = 8.4 Hz), 5.90 (1H, d, *J* = 10 Hz), 5.79 (1H, dd, *J* = 10, 4 Hz), 5.47 (1H, dd, *J* = 8, 6 Hz), 4.20 (1H, t, *J* = 4.3 Hz), 4.11 (1H, m), 3.85 (3H, s), 3.80 (1H, bs), 3.67 (1H, m), 3.46 (1H, dt, *J* = 10, 5 Hz), 2.84-3.02 (3H, m), 2.53 (1H, dd, *J* =

13, 4.2 Hz), 2.10-2.30 (3H, m), 1.96 (1H, d, *J* = 10 Hz), 1.62 (1H, dd, *J* = 13, 8 Hz), 1.23 (3H, t, *J* = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 134.0, 128.4, 127.9, 126.6, 121.5, 111.5, 99.3, 64.0, 61.7, 56.3, 56.2, 56.1, 43.0, 39.0, 38.2, 32.7, 26.8, 15.0. HRMS calcd. for $C_{19}H_{26}NO_5$ [MH^+] 348.1811, found 348.1815.

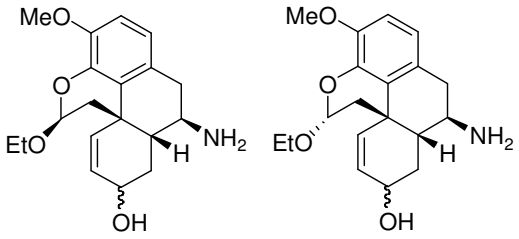
Nitrone 91



To a solution of the hydroxylamine **90b** (100 mg, 0.29 mM) in dioxane (10 mL) was added 2.5 N HCl (3 mL) and the solution was heated at reflux for 2.5 h. The reaction mixture was poured into cold water (10 mL) and basified to pH~8 with 1N NaOH. The resulting solution was extracted with EtOAc (4 x 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow solid (56 mg, 65% yield). Spectral data was obtained without purification.

R_f = 0.62 (10% MeOH/$CHCl_3$). IR (thin film) 3100, 2973, 2930, 1652, 1506, 1457, 1276, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, t, *J* = 3.6 Hz), 6.77 (1H, d, *J* = 8.3 Hz), 6.61 (1H, d, *J* = 8.3 Hz), 5.87 (1H, m), 5.76 (1H, m), 5.07 (1H, s), 3.85 (3H, s), 3.02 (1H, d, *J* = 18.5 Hz), 3.00 (1H, dd, *J's* = 18.5, 5.7 Hz), 2.82 (1H, s), 2.68-2.79 (3H, m), 2.05 (1H, dt, *J* = 18, 6 Hz), 1.57 (1H, dd, *J* = 15, 4 Hz). ^{13}C NMR could not be obtained due to dimerization of the product at high concentrations in the NMR solvent. HRMS calcd. for $C_{17}H_{18}NO_3$ (MH^+) 284.1287, found 284.1289.

12-Amino-6-ethoxy-8-methoxy-1,5,6,11,12,12a-hexahydro-2H-naphtho[8a,1,2-de]chromen-2-ol 92a/92b.



92a **92b**

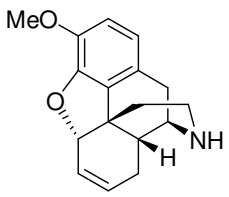
To a solution of the nitroalkanes **81a/81b** (468 mg, 1.3 mmol) in THF (15 ml) cooled to -78 °C under argon, was added $LiAlH_4$ (2M in THF, 3.9 mL) drop-wise over 20 min. The resulting solution was stirred at -78 °C for 1 h and allowed to warm to R.T over 8h. The reaction was checked for completion, judged by TLC, and then added to saturated aqueous Na_2SO_4 (5 ml) at 0 °C. The salts were filtered through a Buchner funnel and washed with (100 ml) of ether. The organic layer was washed with brine (15 ml), dried (Na_2SO_4), and concentrated *in vacuo* to yield a pale yellow foamy solid. The crude product was purified by column chromatography only for the purpose of characterization. (SiO_2, 1% NEt_3, 10% MeOH, 89% CH_2Cl_2) to yield a white foamy solid (312 mg, 72%).

Data for **92a**. R_f = 0.21 (15% MeOH/CH_2Cl_2). IR (thin film) 3342, 3287, 2924, 2856, 1493, 1441, 1375, 1260, 1210, 1123, 1035, 1009 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (1H, d, *J* = 8.2 Hz), 6.68 (1H, d, *J* = 8.2 Hz), 5.89 (1H, dt, *J's* = 10.4, 2.2 Hz), 5.63 (1H, dt, *J* = 10.2, 1.6 Hz), 5.39 (1H, dd, *J's* = 4, 2 Hz), 4.42-4.38 (1H, m), 3.87 (3H, s), 3.70-3.63 (1H, m), 3.26 (1H, q, *J* = 5 Hz), 2.97 (1H, dd, *J's* = 15, 4 Hz), 2.48 (1H, dd, *J's* = 13.5, 2 Hz), 2.40 (2H, m), 1.98 (2H, dd, *J's* = 13.4, 4 Hz), 1.93-1.86 (3H, m),

1.58 (1H, m), 1.21 (3H, t, *J* = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 140.5, 135.9, 128.2, 127.2, 125.6, 120.8, 110.4, 97.7, 64.4, 64.2, 56.1, 50.5, 49.8, 42.2, 38.4, 34.7, 33.2, 15.2. HRMS calcd. for $C_{19}H_{26}NO_4$ (MH^+) 332.1859, found 332.1856.

Data for **92b**. R_f = 0.26 (15% MeOH/CH_2Cl_2) IR (thin film) 3352, 3287, 2924, 1497, 1439 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (1H, d, *J* = 8.3 Hz), 6.65 (1H, d, *J* = 8.3 Hz), 5.88 (1H, d, *J* = 10 Hz), 5.83 (1H, dd, *J's* = 10, 4 Hz), 5.50 (1H, dd, *J's* = 8, 6 Hz), 4.12 (1H, d, *J* = 4 Hz), 4.10 (1H, m), 3.84 (3H, s), 3.67 (1H, m), 3.41 (1H, td, *J's* = 11, 4 Hz), 2.90 (1H, dd, *J's* = 15.5, 4.5 Hz), 2.61-2.54 (5H, m), 2.38 (1H, dd, *J's* = 15.5 ,2.4 Hz), 2.13 (1H, ddd, *J's* = 15.5, 5, 3 Hz), 1.65 (1H, d, *J* = 10 Hz), 1.59 (1H, dd, *J's* = 13, 8.3 Hz), 1.21 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 141.7, 133.2, 129.6, 128.9, 126.4, 121.2, 111.5, 99.5, 63.9, 61.7, 56.3, 46.9, 43.3, 43.1, 39.9, 38.6, 26.4, 15.1.

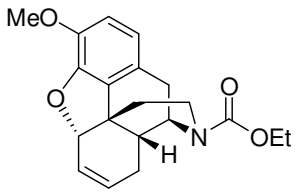
Core secondary amine 93.



To a solution of the primary amines **92a/92b** (1.0 g, 3.02 mM) in dioxane (48 mL) was added 1N HCl (16 mL) and stirred for 10 min. $NaCNBH_3$ (569 mg, 9.06 mM) was added in 3 portions after every 1 h. The mixture was taken to reflux and heated at reflux for 5 h. The pH was maintained between 2-3 by adding 1N HCl as required. The reaction was checked for completion, judged by TLC, cooled to r.t. and basified to pH 9 with 1M NaOH (aq.) and extracted with diethyl ether (5 x 25 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a brown syrup (730 mg). The crude product was purified by column chromatography only for the purpose of characterization (SiO_2, 1% NEt_3, 10% MeOH, 89% CH_2Cl_2) to yield pure **93** as a colorless syrup (540 mg, 66% yield).

R_f = 0.12 (15% MeOH/CH_2Cl_2). IR (thin film) 3307, 3024, 2920, 2847, 1634, 1504, 1439, 1278, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.71 (1H, d, *J* = 8 Hz), 6.30 (1H, d, *J* = 8 Hz), 5.86 (1H, m), 5.71 (1H, m), 4.93 (1H, s), 3.86 (3H, s), 3.43 (1H, m), 3.00 (1H, dd, *J's* = 12, 6 Hz), 2.84 (2H, m), 2.76 (1H, d, *J* = 18 Hz), 2.35 (1H, m), 1.96 (1H, t, *J* = 6 Hz), 1.90 (1H, t, *J* = 6 Hz), 1.80 (1H, m), 1.45 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 143.1, 131.9, 129.5, 127.1, 124.5, 118.4, 112.7, 87.7, 56.1, 51.9, 49.9, 41.5, 39.1, 38.8, 30.7, 24.4. HRMS calcd. for $C_{17}H_{20}NO_2$ (MH^+) 270.1494, found 270.1498.

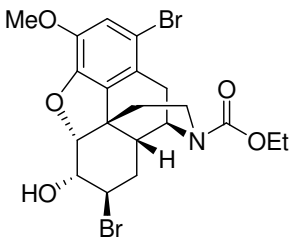
Ethyl carbamate 94.



To a solution of the secondary amine **93** (0.70 g, 2.6 mmol) in CH_2Cl_2 (20 ml) cooled to 0 °C was added triethylamine (1.81 mL, 13.0 mmol) and ethyl chloroformate (0.62 mL, 6.5 mmol) dropwise over 2 min. The resulting solution was stirred at 0 °C for 1 hour. After checking for completion by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with brine (25 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a pale yellow oil. The crude product can be purified by column chromatography (SiO_2, 30% EtOAc/hexanes) to yield **94** as colorless syrup (0.795 g, 90% yield).

R_f = 0.48 (30% EtOAc/hexanes). IR (thin film) 2978, 2931, 2838, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8 Hz), 6.62 (1H, d, *J* = 8 Hz), 5.85 (1H, m), 5.71 (1H, d, *J* = 10 Hz)), 4.95 (1H, s), 4.71 (major amide rotamer 0.60 H, bs), 4.56 (minor amide rotamer 0.4 H, bs), 4.15 (2H, q, *J* = 7.2 Hz), 4.1-3.93 (1H, m), 3.85 (3H, s), 3.06-2.86 (2H, m), 2.68 (1H, d, *J* = 18 Hz), 2.30-2.25 (1H, m), 2.00 (1H, dt, *J's* = 18, 6 Hz), 1.90-1.70 (2H, m), 1.53-1.40 (1H, m), 1.27 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ155.4, 144.9, 143.4, 131.9, 128.5, 125.8, 124.4, 118.9, 113.3, 87.4, 61.4, 56.2, 50.1, 41.1, 37.7, 35.0, 28.8, 24.0, 14.7. Minor rotamer: δ 155.0, 144.8, 143.4, 131.6, 128.5, 125.6, 124.6, 118.9, 113.3, 87.4, 61.4, 56.2, 50.5, 41.1, 37.7, 34.8, 29.0, 24.1, 14.6. HRMS calcd. for $C_{20}H_{24}NO_4$ (MH^+) 342.1705, found 360.1699. Data compared with identical compound reported by Taber.[5]

Bromohydrin 99

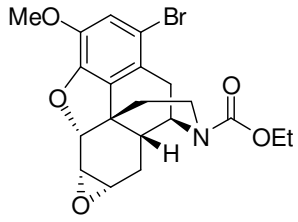


To a solution of **94** (250 mg, 0.73 mmol) in acetone/H_2O (10:1, 11 mL) was added recrystallized 2,2 bromo-3,5 dimethylhydantoin (520 mg, 1.83 mmol) in small portions over 5 min. The entire set-up was covered with aluminum foil, placed in the dark and stirred for 12 h until all the starting material was consumed, as judged by TLC. The reaction mixture was quenched with saturated NH_4Cl (10 ml), diluted with water (10 ml) and extracted with ethyl acetate (3 x 15 ml). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The crude product can be purified by column chromatography (SiO_2, 50 % EtOAc/hexanes) to yield **99** as colorless syrup (365 mg, 97%), or **99** can be carried forward into the next step without purification.

R_f = 0.26 (1:1 EtOAc/hexanes). IR (thin film) 3420, 2978, 2937, 2889, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, s), 4.83 (1H, d, *J* = 7 Hz), 4.78 (Major rotamer 0.60 H, bs), 4.63 (Minor rotamer 0.4 H, bs), 4.11 (2H, q, *J* = 7.2 Hz), 4.1-3.94 (1H, m), 3.89 (3H, s), 3.72-2.59 (2H, m), 2.77-2.61 (1H, m), 2.52 (1H, bs), 2.00 (1H, dt, *J's* = 17, 3.7 Hz), 2.20 (1H, m), 1.75-1.70 (1H, m), 1.27 (3H, t, *J* = 7.2 Hz); 1.07-0.95 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ155.4, 145.1, 143.3, 129.3, 125.2, 117.7, 113.5, 95.8, 70.5, 61.8, 60.4, 56.8, 50.2, 45.4, 38.4, 37.8, 34.4, 31.9, 29.8, 14.6. Minor rotamer: δ 155.0, 145.1, 143.3, 129.3, 125.2, 117.7, 113.5, 95.8, 70.2, 61.7, 60.4, 56.8,

50.6, 45.4, 38.3, 38.2, 34.1, 31.9, 30.1, 14.7. HRMS calcd. for $C_{20}H_{24}NO_4Br_2$ (MH^+) 516.0021, found 516.0018.

Epoxide 100



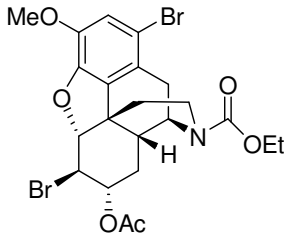
To a solution of the bromohydrin **99** (365 mg, 0.71 mM) in toluene (15 mL) was added solid KOH (200 mg) and the mixture was heated at 80 °C for 3 hours until all the starting material was consumed, as judged by TLC. The reaction mixture was cooled and diluted with water (15 ml) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4) and conc. *in vacuo* to give a yellow oil. The crude product was purified by column chromatography (SiO_2, 40 % EtOAc/hexanes) to yield **100** as a colorless syrup (295 mg, 96%).

R_f = 0.37 (1:1 EtOAc/hexanes). IR (thin film) 2963, 2926, 2850, 1695, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (1H, s), 4.87 (1H, d, *J* = 3.7 Hz), 4.70 (major amide rotamer 0.70 H, bs), 4.56 (minor amide rotamer 0.3 H, bs), 4.13 (2H, q, *J* = 7.3 Hz), 4.1-3.89 (1H, m), 3.86 (3H, s), 3.30-2.23 (2H, m), 2.79-2.70 (2H, m), 2.53 (1H, d, *J* = 18 Hz), 2.00 (2H, m), 1.79-1.68 (2H, m), 1.27 (3H, t, *J* = 7.2 Hz); 1.15-1.06 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ155.2, 146.1, 142.9, 129.2, 124.2, 116.7, 112.0, 87.6, 61.4, 56.4, 53.5, 50.9, 49.8, 41.1, 37.3, 36.2, 35.9, 29.9, 22.7, 14.5. Minor rotamer: δ 154.8, 146.1, 142.9, 129.2, 124.0, 116.7, 112.0, 87.6, 61.5, 56.5, 53.5, 50.9, 50.2, 41.1, 37.2, 36.3, 35.9, 30.2, 22.9, 14.6. HRMS calcd. for $C_{20}H_{23}BrNO_5$ (MH^+) 436.0760, found 436.0758.

Alternative Procedure to obtain the epoxide 100.

To a solution of the carbamate **94** (70 mg, 0.205 mM) in 1,4 dioxane (3 mL) and water (1 mL) was added recrystallized 1,3 bromo-5,5 dimethyl hydantoin (60.0 mg, 0.21 mM) and stirred for 12h in the dark. After **94** was consumed, as judged by TLC, solid KOH (50 mg) was added and the solution was heated at 80 °C for 2.5 h. After all the intermediate bromohydrin **99** was consumed, as judged by TLC, the solution was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by column chromatography (SiO_2, 40% EtOAc/hexanes) to yield **100** as a colorless syrup (81 mg, 91% from **94**).

Acetoxybromide 102

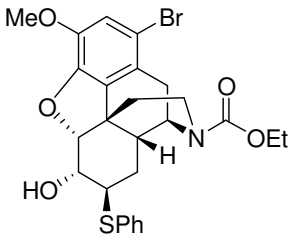


To a solution of the ethylcarbamate **94** (50 mg, 0.12 mM) in acetic acid (1 mL), was added 1,3-dibromo-5,5-dimethylhydantoin (17 mg, 0.06 mM) and the solution was stirred in the dark for 12h at room temperature. After complete consumption of starting material , as judged by TLC, the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 10 mL). the combined organics were washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow liquid. The crude product was purified using flash column chromatography (SiO_2, 30% EtOAc/Hexanes) to give pure **102** as a colorless crystalline solid upon standing (59 mg, 89% yield).

R_f = 0.31 (7:3 Hexanes/EtOAc). M. P. = 112-115 °C. IR (thin film) 2975, 2938, 1740, 1690, 1653, 1489, 1430, 1374, 1226, 1143, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, s), 4.91 (1H, m), 4.85 (1H, d, *J* = 7.4 Hz), 4.77 (Major rotamer 0.60 H, bs), 4.61 (Minor rotamer 0.4 H, bs), 4.16 (2H, m), 4.11-3.91 (1H, m), 3.89 (3H, s), 3.65 (1H, dd, *J* = 11.3, 7.4 Hz), 2.73-2.63 (2H, m), 2.23 (1H, dt, *J's* = 12, 4 Hz), 2.02 (3H, s), 1.98 (1H, d, *J* = 13 Hz), 1.75-1.63 (2H, m), 1.27 (3H, m), 1.03 (1H, q, *J* = 12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ 169.6, 155.3, 145.1, 143.3, 129.2, 125.1, 117.8, 113.5, 95.9, 71.2, 61.7, 61.6, 56.8, 54.1, 50.0, 45.1, 38.1, 37.7, 34.4, 30.7, 20.8, 14.6. Minor rotamer: δ 169.8, 154.9, 145.1, 143.3, 129.2, 124.8, 117.8, 113.4, 95.9, 71.4, 61.8,

61.6, 56.8, 53.9, 50.4, 45.1, 38.0, 37.7, 34.1, 30.7, 20.8, 14.7. HRMS calcd. for $C_{22}H_{26}NO_6Br_2$ (MH^+) 558.0127, found 558.0114.

Phenyl sulfide 106

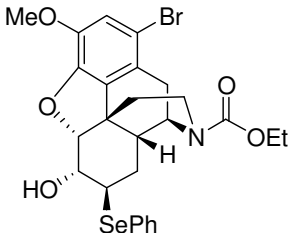


To a solution of diphenyl disulfide (12 mg, 0.055 mmol) in EtOH (1.0 mL) was added $NaBH_4$ (4 mg, 0.11 mmol) portion-wise over 5 min. The resulting solution was stirred for 15 min and then added drop-wise to a solution of the epoxide **100** (16 mg, 0.037 mmol) in EtOH (1.0 mL). The reaction mixture was stirred at 25 °C for 2 h until all the substrate was consumed, as judged by TLC. The mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4) and conc. *in vacuo* to give a pale yellow solid. The crude product was purified by column chromatography (SiO_2, 30% EtOAc/hexanes) to yield **106** as a white solid (20 mg, 99% yield).

R_f = 0.60 (40% EtOAc/hexanes). IR (thin film) 3446, 2936, 1684, 1487, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 7.3 Hz), 7.30 (3H, m), 6.93 (1H, s), 4.88 (1H, d, *J* = 5 Hz), 4.69 (Major rotamer 0.60 H, bs), 4.54 (Minor rotamer 0.4 H, bs), 4.14 (2H, q, *J* = 7.2 Hz), 4.07-3.91 (2H, m), 3.84 (3H, s), 3.36-3.28 (1H, m), 2.79-2.59 (2H, m), 2.39-2.34 (2H, m), 1.85-1.56 (4H, m), 1.27 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ155.3, 145.8, 142.8, 132.3, 129.2, 127.7, 125.1, 116.6, 112.8, 89.0, 68.4, 61.5, 60.3, 56.4, 50.5, 46.5, 42.5, 37.6, 36.2, 36.0, 29.9, 24.4, 21.0, 14.6; Minor rotamer: δ 155.0, 145.8, 142.8, 133.2, 132.0, 130.7, 129.2, 127.7, 124.8, 116.6,

112.8, 89.0, 68.4, 61.6, 56.4, 51.0, 46.5, 42.3, 37.6, 36.4, 35.7, 30.1, 24.4, 14.7; HRMS calcd. for $C_{26}H_{29}BrNO_5S$ (MH^+) 546.0950, found 546.0958.

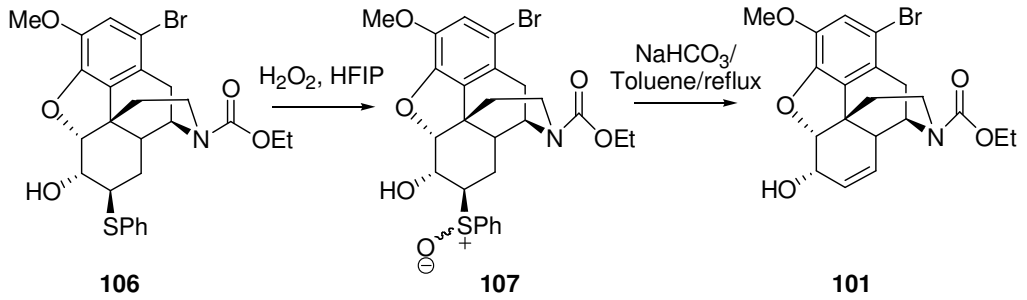
Phenylselenide 104



Procedure is the same as that used for the phenylsulfide **106**, except diphenyldiselenide is used in this case. Yield (93%).

Rf = 0.32 (40% EtOAc/hexanes). IR (thin film) 3447, 2917, 2849, 1695, 1684, 1489, 1437, 1319, 1289, 1228 cm-1. 1H NMR (300 MHz, CDCl3) □ 7.53 (2H, d, J = 6.6 Hz), 7.30 (3H, m), 6.94 (1H, s), 4.95 (1H, d, J = 5.2 Hz), 4.70 (Major rotamer 0.60 H, bs), 4.55 (Minor rotamer 0.4 H, bs), 4.16 (2H, q, J = 7.0 Hz), 4.03-3.98 (2H, m), 3.86 (3H, s), 3.36-3.28 (1H, m), 2.80-2.70 (2H, m), 2.63 (1H, d, J = 18 Hz), 2.29 (2H, m), 1.85-1.75 (2H, m), 1.66-1.55 (2H, m), 1.27 (3H, t, J = 7.2 Hz). HRMS calcd. for $C_{26}H_{29}NO_5SeBr$ (MH+) 594.0394, found 594.0387.

Allylic alcohol 101.



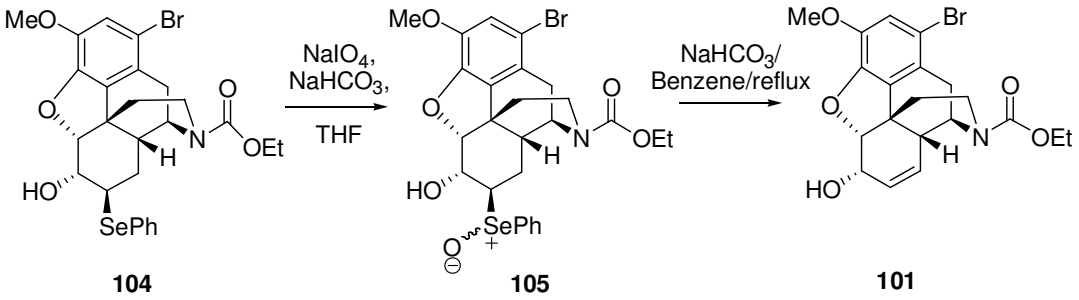
To a solution of **106** (20 mg, 0.036 mmol) in hexafluoroisopropanol (0.5 mL) was added hydrogen peroxide (30% aq., 0.05mL) and the resulting solution was stirred for 15 min until all starting material was consumed, as judged by TLC. The reaction mixture was diluted with water (5 ml) and quenched with saturated aqueous Na_2SO_3 (2 mL) and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and conc. *in vacuo* to give a pale yellow solid. The crude product (**107**) was dissolved in toluene (2 mL) and solid $NaHCO_3$ (15 mg) was added. The mixture was heated at reflux for 2 h until all the intermediate sulfoxide had been consumed. The reaction was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and conc. *in vacuo* to give a pale yellow syrup. The crude product was purified by column chromatography (SiO_2, 50% EtOAc/hexanes) to yield a colorless syrup (14 mg) as a mixture of **101** (76 % yield) along with the saturated ketone **108** (17%).

R_f = 0.60 (40% EtOAc/Hexanes). IR (thin film) 3446, 2978, 2932, 2868, 1684, 1489, 1435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (1H, s), 5.77 (1H, d, *J* = 8.8 Hz), 5.30 (1H, dd, *J* = 6.6, 1.5 Hz), 5.02 (Major rotamer 0.60 H, bs), 4.90 (1H, d, J = 6.6 Hz),

4.88 (Minor rotamer 0.4 H, bs), 4.14 (2H, q, *J* = 7.2 Hz), 3.84 (3H, s), 2.96-2.84 (2H, m), 2.78-2.66 (3H, m), 2.60-2.52 (1H, d, *J* = 21 Hz), 2.45-2.41 (1H, m), 1.95-1.87 (4H, m), 1.27 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ155.4, 145.9, 143.3, 134.4, 131.3, 126.9, 125.5, 116.2, 113.3, 91.4, 66.0, 56.4, 50.3, 47.8, 43.8, 39.3, 37.2, 35.3, 29.7, 14.6; Minor rotamer: δ 155.0, 145.9, 143.3, 134.7, 131.3, 126.8, 125.3, 117.7, 113.5, 91.4, 61.7, 56.8, 49.9, 47.8, 41.1, 39.7, 37.7, 34.9, 29.9, 14.7. HRMS calcd. for $C_{20}H_{22}BrNO_5Na$ ($M+Na^+$) 458.0579, found 458.0577.

The minor product corresponding to the saturated ketone **108** can be identified by the following signals. R_f = 0.61 (40% EtOAc/Hexanes). IR (thin film) 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (0.23 H, s), 4.60 (0.23 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5. HRMS calcd. for $C_{20}H_{23}BrNO_5$ (MH^+) 436.0760, found 436.0761.

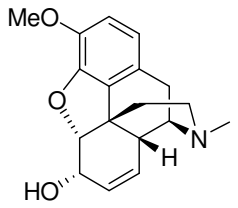
Selenide oxidation-elimination.



104 **105** **101**

To a solution of the selenide **104** (25 mg, 42 μM) in THF (2.0 mL) and saturated aqueous $NaHCO_3$ (2 mL) was added a solution of $NaIO_4$ (225 mg) in H_2O (1 mL) in a single portion. The mixture was stirred for 45 min and then filtered over Celite® and washed repeatedly with DCM. The combined organics were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid (**105**) was dissolved in benzene (5 mL) and saturated aqueous $NaHCO_3$ (1 mL) and heated at reflux for 1 h until all the intermediate had been consumed, as judged by TLC. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 ml) and the organic layers were separated. The combined organic layers were washed were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a colorless oil. The crude product was purified by column chromatography (SiO_2, 50% EtOAc/hexanes) to yield **101** as a colorless syrup (14 mg, 77% yield).

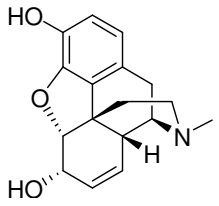
(±)-Codeine 3.



To the allylic alcohol **101** (10 mg, 0.023 mM), in THF (1.5 mL) was added $LiAlH_4$ (2M in THF, 0.3 mL) and the solution was stirred at 25 °C for 6 h. The reaction mixture was cooled to 0 °C and quenched with drop-wise addition of saturated aqueous Na_2SO_4 (0.5 mL). The salts were filtered over a pad of Celite and washed with diethyl ether (10 mL). The combined organics were dried (Na_2SO_4) and evaporated *in vacuo* to yield a pale yellow solid. The crude product was purified (SiO_2, 10% MeOH/CH_2Cl_2) to give codeine **3** (6 mg, 87%).

R_f = 0.21 (10% MeOH/CH_2Cl_2). M.p. 151-153 °C. IR (thin film) 3283, 2962, 2917, 2851, 1506, 1456, 1472, 1261, 1089, 1048, 1020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (1H, d, *J* = 8.1 Hz), 6.57 (1H, d, *J* = 8.8 Hz), 5.71 (1H, d, *J* = 9.5 Hz), 5.30 (1H, dt, *J* = 10.3, 2.2 Hz), 4.90 (1H, dd, *J* = 6.6 Hz), 4.19 (1H, m), 3.85 (3H, s), 3.36 (1H, dd, J = 6, 3 Hz), 3.06 (1H, d, *J* = 19.1 Hz), 2.69 (1H, s), 2.60 (1H, dd, *J* = 12.5, 3.7 Hz), 2.45 (3H, s), 2.39 (1H, dd, *J* = 12.5, 3.7 Hz), 2.31 (1H, dd, *J* = 18.4, 5.9 Hz), 2.03-2.12 (1H, m), 1.86-1.90 (1H, m), 1.26 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 142.2, 133.4, 131.0, 128.2, 127.2, 119.5, 112.8, 91.3, 66.4, 58.8, 56.3, 46.4, 43.1, 40.7, 35.8, 29.8, 20.3. HRMS calcd. for $C_{18}H_{22}NO_3$ 300.1600, found 300.1601.

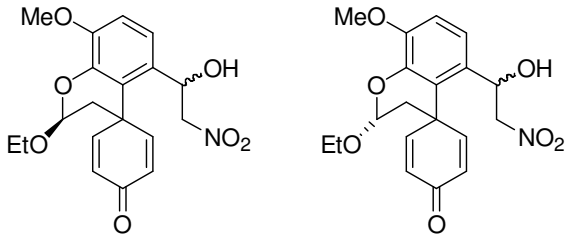
Morphine 1



To a solution of codeine **3** (8 mg, 0.026 mM) in chloroform (2.5 mL), was added boron tribromide (1.0 M in DCM, 0.20 mmol) dropwise over 1 min and the resulting mixture was stirred at room temperature for 20 min. A solution of NH_4OH (10 % aq., 10 mL) was added dropwise at 0 °C and the mixture was extracted with a solution of 9:1 DCM/EtOH (4 x 15 mL). The combined organics were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified (SiO_2, 1:9 MeOH/DCM) to give morphine **1** (6.5 mg, 86% yield) as a white solid. R_f = 0.06 (1:9 MeOH/DCM). M.p. 251-255 °C. IR (thin film) 3352, 2924, 1459, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDC1_3$) δ 6.62 (1H, d, *J* = 8.1 Hz), 6.48 (1H, d, *J* = 8.1 Hz), 5.67 (1H, d, *J* = 9.9 Hz), 5.27 (1H, dt, *J* = 9.9, 2.6 Hz), 4.84 (1H, dd, *J* = 6.3 Hz), 4.18 (1H, m), 3.84 (3H, s), 3.36 (1H, m), 3.03 (1H, d, *J* = 18.6 Hz), 2.66 (1H, m), 2.60 (1H, d, *J* = 4.5 Hz), 2.47 (1H, dd, *J* = 24.3, 3.6 Hz), 2.46 (1H, s), 2.34 (1H, dd, *J* = 18.9, 6.3 Hz), 2.06 (1H, dt, *J* = 12.9, 5.1 Hz), 1.90 (1H, d, *J* = 12.9 Hz). ^{13}C NMR (75 MHz, $CDC1_3$) δ 145.6, 138.1, 132.7, 130.4, 127.9, 125.5, 119.5, 116.8, 91.1, 66.2, 58.7, 46.2, 42.7, 42.4, 40.0, 34.8, 20.4. HRMS calcd, for $C_{17}H_{20}NO_3$ (MH^+) 286.1443, found 286.1445.

4.2 EXPERIMENTAL CONDITIONS AND COMPOUND DATA FOR CHAPTER 2

Uncyclized nitroalcohols 119a/119b



119a **119b**

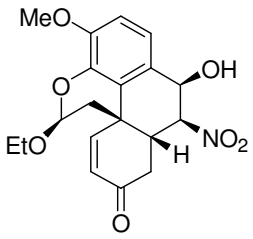
To nitromethane (0.04 mL) in THF (0.5 mL) at -78 °C under argon, was added *n*-butyllithium (0.03 mL, 2.5 M in hexanes) and the mixture was stirred for 15 min. To this slurry, a solution of the dienone **60** (25 mg, 0.08 mM) in THF (0.5 mL) was added drop-wise over 1 min. The mixture was stirred for an additional 30 h at -78 °C after which all the starting material had been consumed, as judged by TLC. The reaction mixture was quenched with saturated NH_4Cl (2 mL) and extracted with ether. Flash column chromatography (SiO_2, 30% EtOAc/Hexanes) separated the two compounds; each a colorless foam (22 mg, 74% combined yield).

Data for **119a**: R_f = 0.20 (1:1 EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J's* = 10, 3 Hz), 7.20 (1H, d, *J* = 9 Hz), 6.99 (1H, *J's* = 10, 3 Hz), 6.96 (1H, d, *J* = 9 Hz), 6.46 (1H, dd, *J*'s = 8, 2 Hz), 6.30 (1H, dd, *J's* = 8, 2 Hz), 5.51 (1H, d, *J* = 12 Hz), 5.46 (1H, t, *J* = 2 Hz), 4.46 (1H, dd, *J's* = 18, 12 Hz), 4.21 (1H, dd, *J's* = 18, 2 Hz), 4.00 (s, 3H), 3.87 (1H, m), 3.65 (1H, m), 3.04 (1H, bs), 2.38 (1H, dd, *J's* = 14, 2 Hz), 1.94 (1H, dd, *J's* = 14, 2 Hz), 1.18 (3H, t, *J* = 7 Hz).

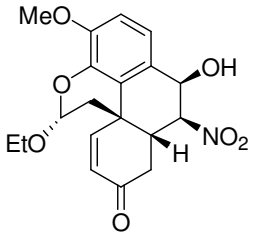
Data for **119b**: R_f = 0.25 (1:1 EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J's* = 10, 3 Hz), 7.04 (1H, *J's* = 10, 3 Hz), 6.98 (1H, d, *J* = 9 Hz), 6.38 (1H, dd, *J*'s = 8, 2 Hz), 6.36 (1H, dd, *J's* = 8, 2 Hz), 5.5 (1H, t, *J* = 2 Hz), 5.42 (1H, m), 4.60 (1H, t, *J* = 18 Hz), 4.52 (1H, dd, *J's* = 18, 12 Hz), 4.00 (s, 3H), 3.96 (1H, m), 3.70 (1H, m), 2.89 (1H, d, *J* = 14 Hz), 2.21 (1H, dd, *J's* = 14, 2 Hz), 1.96 (1H, dd, *J's* = 14, 2 Hz), 1.25 (3H, t, *J* = 7 Hz).

^{13}C NMR could not be obtained due to rapid cyclization of the compounds to the respective nitroalcohols **114a/114b**. HRMS was therefore identical to the data reported for **114a/114b**.

6-Ethoxy-11-hydroxy-8-methoxy-12-nitro-1,5,6,11,12,12a-hexahydro-naphtho[8a,1,2-de]chromen-2-one, 114a/114b.



114a



114b

To a solution of the dienone **60** (20 mg, 0.064 mM) in toluene (0.5 mL) at -20 °C, was added the phase-transfer catalyst (8*S*, 9*R*)-(-)-*N*-Benzylcinchonidinium chloride (M.P. 209 °C)(8mg) followed by flame-dried Cs_2CO_3 (20 mg, 0.064 mM) and nitromethane (0.05 mL, 0.94 mM) and the solution was stirred for 24h until all the dienone had been consumed , as judged by TLC. The reaction mixture was diluted with ether (5 mL), quenched with saturated NH_4Cl (2 mL) and extracted with ether (3 x 5 mL). The combined organics were washed with bring (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow solid. The products were purified via column chromatography (SiO_2, 40% EtOAc/Hexanes) to give the two title compounds as white crystalline solids in approximately 1:1 ratio. (Combined: 14.2 mg, 60% yield).

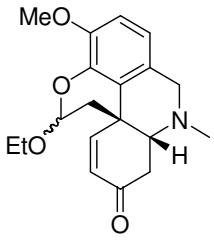
Data for compound **114a**: R_f = 0.37 (1:1 EtOAc/hexanes). M.p. 210 °C. $[\alpha]_D^{24.5}$= -200.0° (c = 1.0 CH_2Cl_2). IR (thin film) 3481, 2975, 2931, 1675, 1555, 1442, 1344, 1267, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (1H, d, *J* = 8.9 Hz), 6.99 (1H, dd, *J*'s = 10, 2 Hz), 6.97 (1H, d, *J* = 8 Hz), 5.98 (1H, d, *J* = 10 Hz), 5.56 (1H, t, *J* = 1.5 Hz), 5.12 (1H, t,

J = 6.1 Hz), 5.00 (1H,t, *J* = 6 Hz), 3.98 (3H, s), 3.92 (1H, m), 3.70 (1H, m), 3.00 (1H, dd, *J* = 18, 5.2 Hz), 2.89 (1H, m), 2.78 (1H, s), 2.74 (1H, d, *J* = 9 Hz), 2.62 (1H, dd, *J's* = 13.2, 1.5 Hz), 2.23 (1H, dd, J = 13.2, 3 Hz), 1.21 (3H, t, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 154.4, 148.6, 139.1, 127.9, 127.6, 120.9, 116.4, 111.2, 95.6, 92.3, 68.7, 64.4, 60.4, 56.1, 42.2, 40.4, 35.6, 34.9, 29.7, 15.1. HRMS calcd. for $C_{19}H_{20}NO_7$ ($M\text{-}H^+$) 374.1245, found 375.1243.

Data for compound **114b**: R_f = 0.42 (1:1 EtOAc/hexanes). M.p. 188-190 °C. $[\alpha]_D^{25.4}$= +154.9° (c = 1.0 CH_2Cl_2). IR (thin film) 3420, 2976, 2932, 1683, 1553, 1502, 1440, 1344, 1279, 1047 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, d, *J* = 8.1 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 6.79 (1H, dd, *J*'s = 10.3, 1.5 Hz), 6.06 (1H, d, *J* = 10.3 Hz), 5.53 (1H, dd, *J* = 8.1, 6.6 Hz), 5.15 (1H, d, *J* = 2.2 Hz), 4.93 (1H, dd, *J* = 12, 3 Hz), 4.09 (1H, m), 3.89 (3H, s), 3.69 (1H, m), 2.92 (1H, ddd, *J* = 12, 5.2, 2.2 Hz), 2.99-2.85 (3H, m), 2.74 (1H, d, *J* = 18 Hz), 2.05 (1H, dd, *J's* = 13.2, 8.1Hz), 1.21 (3H, t, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 154.4, 148.6, 139.1, 127.9, 127.6, 120.9, 116.4, 111.2, 95.6, 92.3, 68.7, 64.4, 60.4, 56.1, 42.2, 40.4, 35.6, 34.9, 29.7, 15.1.

4.3 EXPERIMENTAL CONDITIONS AND COMPOUND DATA FOR CHAPTER 3

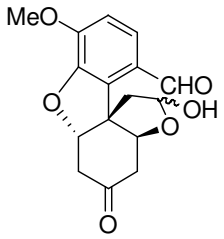
Tetracyclic amine 129a/129b



To a solution of the dienone **60** (100 mg, 0.32 mM) in 1,4-dioxane (1.5 mL) was added methylamine hydrochloride (25.8 mg, 0.38 mM) followed by N,N-diisopropylethylamine (0.07 mL, 0.38 mM) and the solution was stirred at 0 °C for 1h. Sodium cyanoborohydride (30 mg, 0.48 mM) was then added, in small portions, and the solution was stirred for an additional 12h. The reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with ether (4 x 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a colorless syrup. Purification by column chromatography (SiO_2, 50% EtOAc/Hexanes) gave pure **129a/129b** as an inseparable mixture of two diastereomers (86 mg, 82% yield).

R_f 0.37 (1:1 hexanes/EtOAc); IR (thin film) 3364, 2925, 2853, 2784, 1684 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (2H, t, *J* = 9 Hz), 6.65 (1H, d, *J* = 8 Hz), 6.03 (1H, d, *J* = 10 Hz), 5.54 (1H, t, *J* = 7 Hz), 4.14-4.07 (1H, m), 3.85 (3H, s), 3.71-3.65 (1H, m), 3.40 (1H, d, *J* = 15 Hz), 2.85 (1H, dd, *J* = 5, 3 Hz), 2.78 (1H, d, *J* = 5 Hz), 2.72-2.66 (2H, m), 2.37 (3H, s), 1.88 (1H, d, *J* = 13 Hz), 1.86 (1H, d, *J* = 13 Hz), 1.23 (3H, t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 151.8, 147.6, 127.9, 125.4, 125.0, 118.5, 111.8, 110.8, 98.7, 66.2, 64.1, 57.5, 56.1, 41.8, 40.6, 37.7, 29.5, 14.8; HRMS calcd. for $C_{19}H_{24}NO_4$ (MH^+) 330.1705, Found 330.1704.

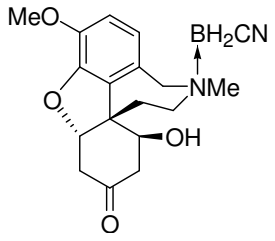
Aldehyde-lactol 131.



1,4-Dioxane (1.5 mL), 1.0 M aqueous HCl (1.5 mL), and the cross-conjugated dienone **60** (0.080 g, 0.255 mmol) were stirred at 23 °C for 1 h until the mixture was homogeneous. The solution was heated for 2 h at reflux until all starting material was consumed, as judged by TLC. The mixture was poured into water (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield **131** as pale yellow-orange foam (0.072 g, 93% yield). Crystallization of **131** from MeCN with slow cooling provided X-ray quality crystals for the purpose of characterization.

R_f 0.28 (1:1 hexanes/EtOAc). M.p. 212 °C. IR (thin film) 3461, 2934, 2908, 2844, 1719, 1679 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (1H, s), 7.56 (1H, d, *J* = 8 Hz), 7.03 (1H, d, *J* = 8 Hz), 6.19 (1H, d, *J* = 9 Hz), 5.65 (1H, t, *J* = 7 Hz), 4.71 (1H, d, *J* = 64 Hz), 4.00 (3H, s), 3.08-2.99 (2H, m), 2.81 (1H, dd, *J* = 41, 3 Hz), 2.80 (1H, dd, *J's* = 6 and 3 Hz), 2.34-2.22 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 192.3, 150.4, 149.4, 133.4, 132.2, 129.5, 125.7, 111.3, 98.1, 89.9, 56.2, 53.7, 46.7, 39.0, 38.1. HRMS calcd. for $C_{16}H_{15}O_5$ ($MH^+ - H_2O$) 287.0919, found 287.0924. Structure of **131** by X-ray shows that the crystals are a mixture of lactol epimers.

β-hydroxyketone 132a

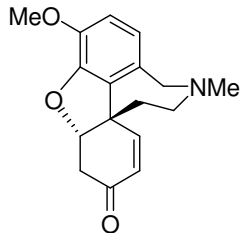


To a solution of the lactol **131** (500 mg, 1.64 mM) in 1,4-dioxane (8 mL) was added recrystallized methylamine hydrochloride (133 mg, 1.97 mM) followed by *N*,*N*-diisopropylethylamine (0.43 mL, 2.46 mM) and the resulting suspension was stirred in a sealed flask for 8 h at r.t. Glacial acetic acid (0.94 mL, 24.6 mM) followed by $NaBH_3CN$ was then added and the suspension was stirred until a single spot was seen on the TLC. The reaction mixture was carefully quenched with aqueous satd. $NaHCO_3$. The aqueous layer was extracted with chloroform (4 x 25 mL) and the combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale brown solid (448 mg, 80% yield). NMR indicated that the crude material was pure enough to be used without further purification. However, material of very high purity can be obtained by flash column chromatography (SiO_2, 10 % MeOH/$CHCl_3$). The compound **132a** was crystallized from toluene and the structure was elucidated by X-ray crystallography.

R_f = 0.43 (9:1 $CHCl_3$/MeOH). M.p. 202 °C. IR (thin film) 3420, 2923, 2847, 2414, 1718, 1507, 1437, 1286 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, d, *J* = 8.2 Hz)), 6.60 (1H, d, *J* = 8.2 Hz), 6.02 (1H, dd, *J's* = 10.4, 0.5 Hz), 5.20 (1H, d, *J* = 3.7 Hz), 4.68 (1H, t, *J* = 3 Hz), 4.41 (1H, d, *J* = 15 Hz), 4.33 (1H, s), 3.86 (1H, d, *J* = 15 Hz), 3.77 (3H, s), 3.66 (1H, t, *J* = 14 Hz), 3.26 (1H, d, *J* = 15 Hz), 2.89 (1H, dd, *J*'s = 18, 3 Hz), 2.84 (1H, dd, *J*'s = 18, 3 Hz), 2.50 (1H, dd, *J*'s = 17.2, 4 Hz), 2.38 (3H, s), 2.34 (1H, d, *J*

= 3), 2.14 (1H, dd, *J*'s = 17, 1.4), 1.92 (1H, t, *J* = 13.1 Hz) ^{13}C NMR (100 MHz, $CDCl_3$ + 5% DMSO-d6) δ 206.8, 146.9, 145.2, 131.1, 124.3, 121.0, 111.9, 88.1, 65.6, 63.5, 59.3, 55.7, 50.3, 43.4, 42.3, 29.5.HRMS calcd. for $C_{18}H_{23}BN_2O_4$ (MH^+) 343.1829, found 343.1827.

Narwedine 56.



To a solution of the crude β-hydroxyketone **132a** (448 mg, 1.47 mM) in 1,4-dioxane (5 mL) was added a 20% solution of methanesulfonic acid in water (0.5 mL). The solution was heated at reflux for 4 h until complete conversion to Narwedine was observed, as judged by TLC. The reaction mixture was cooled to r.t. and quenched with saturated aqueous $NaHCO_3$ to pH ~ 8.5. The aqueous layer was extracted with $CHCl_3$ (4 x 20 mL) and the combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a give (±)-narwedine **56** as a pale brown solid. (338 mg, 88% yield).

R_f 0.35 (9:1 $CHCl_3$/MeOH). M.p. 186 °C. IR (thin film) 2924, 2853, 1683, 1506, 1436, 1283 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, dd, *J's* = 10.4, 1.4 Hz)), 6.69 (1H, d, *J* = 8.2 Hz), 6.62 (1H, d, *J* = 8.2 Hz), 6.02 (1H, dd, *J's* = 10.4, 0.5 Hz), 4.72 (1H, m), 4.07 (1H, d, *J* = 15.5 Hz), 3.82 (3H, s), 3.73 (1H, d, *J* = 15.5 Hz), 3.26-3.10 (3H, m), 2.74 (1H, dd, *J's* = 17.7, 4 Hz), 2.43 (3H, s), 2.26 (1H, td, *J's* = 13.7 and 3.5 Hz), 1.84 (1H, ddd, *J's* = 13.7, 3.5, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 146.9, 144.3, 143.9, 130.5, 129.3, 127.0, 121.9, 111.7, 87.9, 60.6, 55.9, 54.0, 48. 9, 42.4, 37.2, 33.2. HRMS calcd. for $C_{17}H_{20}NO_3$ (MH^+) 286.1443, found 286.1441.

5.4 REFERENCES

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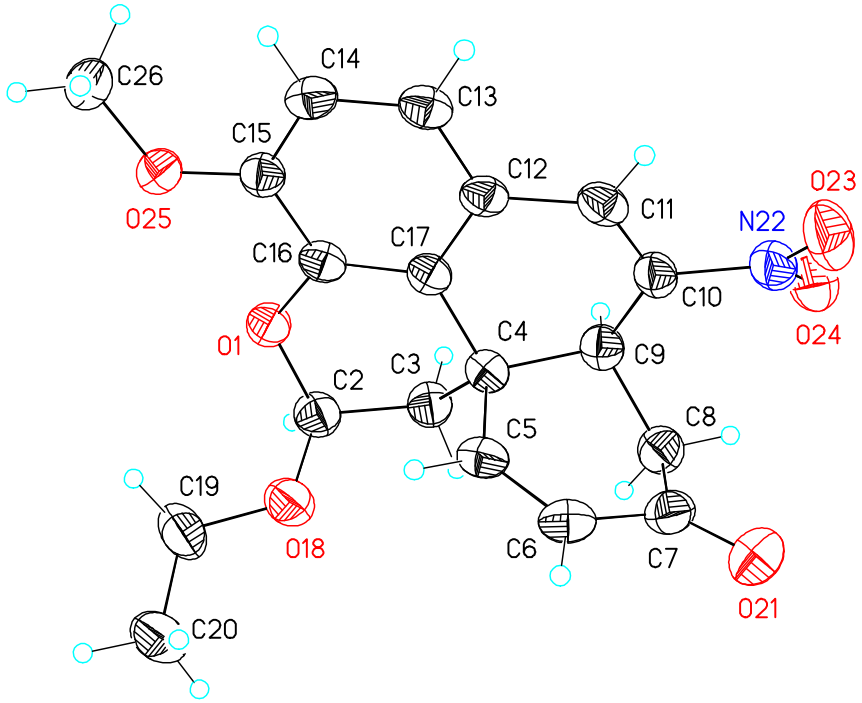
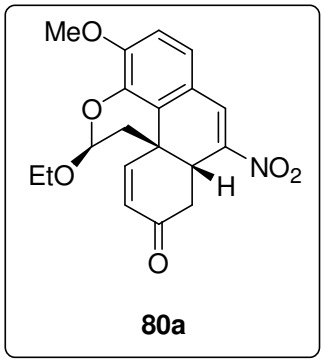
Appendix A: X-ray Data for the nitroalkene 80a

Figure 1. View of the nitroalkene **80a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





80a

X-ray Experimental for nitroalkene 80a

Crystals grew as yellow laths by slow evaporation from dichloromethane and hexanes. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.15 x 0.11 x 0.10 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 199 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 226 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0395*P)^2 + (0.6162*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.131, with R(F) equal to 0.0564 and a goodness of fit, S, = 1.02. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (7.4(10)x10^{-6})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroalkene **80a**.

Empirical formula	C19 H19 N O6	
Formula weight	357.35	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.0662(3) Å	α= 104.467(2)°.
	b = 12.3161(3) Å	β= 90.041(2)°.
	c = 13.8006(5) Å	γ = 118.668(2)°.
Volume	1724.78(9) $Å^3$	
Z	4	
Density (calculated)	1.376 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	752	
Crystal size	0.15 x 0.11 x 0.10 mm	
Theta range for data collection	1.94 to 27.50°.	
Index ranges	-15<=h<=15, -15<=k<=15, -14<=l<=17	
Reflections collected	12233	
Independent reflection	7819 [R(int) = 0.0355]	
Completeness to theta = 27.50°	98.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7819 / 0 / 474	

Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0564, wR2 = 0.1058
R indices (all data)	R1 = 0.1257, wR2 = 0.1313
Extinction coefficient	$7.4(10)x10^{-6}$
Largest diff. peak and hole	0.450 and -0.224 e.$Å^{-3}$

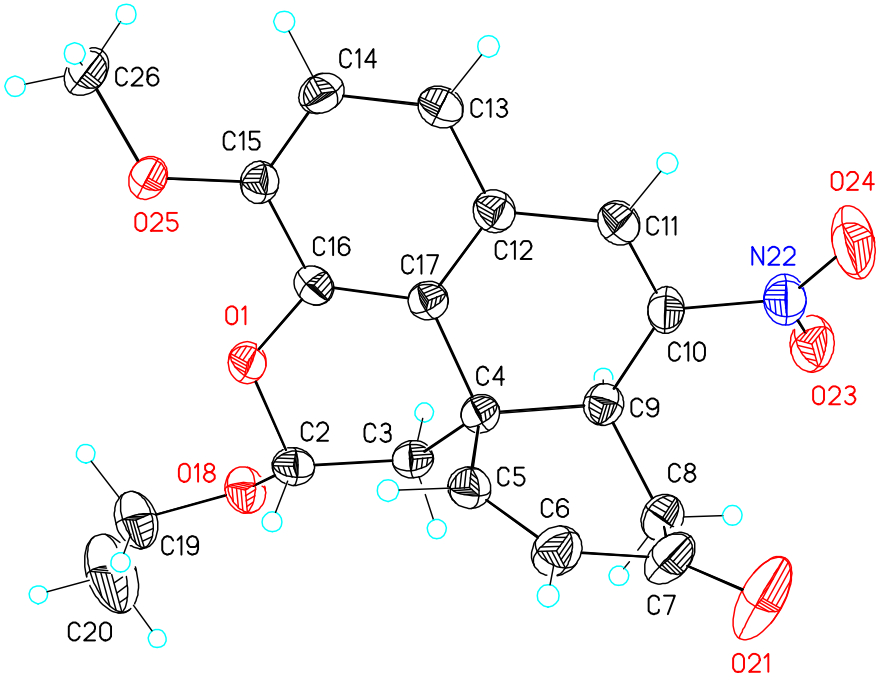
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for nitroalkene **80a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

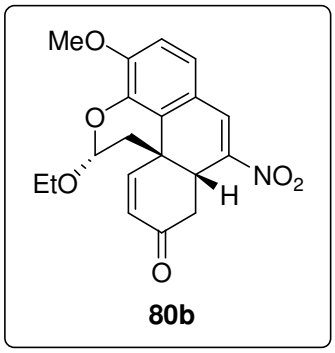
	x	y	z	U(eq)
O1A	6616(1)	6814(2)	6575(1)	40(1)
C2A	7097(2)	7522(2)	5843(2)	38(1)
C3A	8134(2)	8899(2)	6326(2)	35(1)
C4A	9260(2)	9020(2)	6955(2)	30(1)
C5A	10030(2)	8549(2)	6287(2)	33(1)
C6A	11167(2)	9313(2)	6065(2)	39(1)
C7A	11759(2)	10719(2)	6401(2)	42(1)
C8A	10909(2)	11224(2)	6861(2)	38(1)
C9A	10144(2)	10449(2)	7578(2)	31(1)
C10A	10983(2)	10492(2)	8419(2)	31(1)
C11A	10669(2)	9536(2)	8834(2)	32(1)
C12A	9457(2)	8349(2)	8507(2)	29(1)
C13A	9010(2)	7459(2)	9065(2)	36(1)
C14A	7799(2)	6385(2)	8782(2)	37(1)
C15A	7020(2)	6196(2)	7956(2)	36(1)
C16A	7477(2)	7078(2)	7370(2)	32(1)
C17A	8692(2)	8134(2)	7630(2)	28(1)
O18A	7562(2)	6914(1)	5107(1)	39(1)
C19A	6565(2)	5711(2)	4440(2)	49(1)
C20A	7152(3)	5290(2)	3578(2)	55(1)
O21A	12865(2)	11435(2)	6322(2)	64(1)
N22A	12150(2)	11710(2)	8891(1)	39(1)
O23A	13035(2)	11688(2)	9316(1)	51(1)
O24A	12188(2)	12722(2)	8864(1)	47(1)
O25A	5812(2)	5188(2)	7617(1)	49(1)

C26A	5279(3)	4289(3)	8205(2)	64(1)
O1	7973(1)	2791(1)	3196(1)	37(1)
C2	7683(2)	2186(2)	2117(2)	39(1)
C3	6597(2)	818(2)	1839(2)	37(1)
C4	5387(2)	645(2)	2316(2)	31(1)
C5	4768(2)	1295(2)	1908(2)	35(1)
C6	3676(2)	686(2)	1288(2)	39(1)
C7	2996(2)	-724(2)	874(2)	41(1)
C8	3743(2)	-1366(2)	1015(2)	40(1)
C9	4415(2)	-818(2)	2111(2)	34(1)
C10	3479(2)	-1007(2)	2865(2)	33(1)
C11	3721(2)	-186(2)	3778(2)	34(1)
C12	4935(2)	988(2)	4129(2)	31(1)
C13	5261(2)	1729(2)	5130(2)	34(1)
C14	6465(2)	2813(2)	5468(2)	34(1)
C15	7355(2)	3128(2)	4806(2)	32(1)
C16	7020(2)	2391(2)	3783(2)	31(1)
C17	5812(2)	1343(2)	3437(2)	29(1)
O18	7432(2)	2914(2)	1630(1)	46(1)
C19	8578(3)	4114(2)	1635(2)	53(1)
C20	8235(4)	4768(3)	1006(2)	80(1)
O21	1896(2)	-1328(2)	441(1)	59(1)
N22	2293(2)	-2238(2)	2650(2)	43(1)
O23	1360(2)	-2270(2)	3037(2)	59(1)
O24	2287(2)	-3208(2)	2109(1)	53(1)
O25	8564(2)	4135(1)	5061(1)	39(1)
C26	8932(2)	4951(2)	6086(2)	45(1)

Appendix B: X-ray Data for the nitroalkene 80b

Figure 1. View of nitroalkene **80b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





80b

X-ray Experimental for Nitroalkene 80b

Crystals grew as yellow needles by slow evaporation from chloroform. The data crystal was a needle that had approximate dimensions; 0.31 x 0.09 x 0.08 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 238 frames of data were collected using ω-scans with a scan range of 1.9° and a counting time of 146 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0512*P)^2 + (0.5475*P)]$ and $P = (|F_o|^2 + 2|Fc|^2)/3$. $R_w(F^2)$ refined to 0.116, with R(F) equal to 0.0445 and a goodness of fit, S, = 1.00. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (6.1(11)x10^{-6})* F_c^2 \lambda 3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroalkene **80b**.

Empirical formula	C19 H19 N O6	
Formula weight	357.35	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 8.4748(2) Å	α= 90°.
	b = 18.2912(4) Å	β= 95.3460(9)°.
	c = 11.1855(3) Å	γ = 90°.
Volume	1726.37(7) $Å^3$	
Z	4	
Density (calculated)	1.375 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	752	
Crystal size	0.31 x 0.09 x 0.08 mm	
Theta range for data collection	2.14 to 27.49°.	
Index ranges	-10<=h<=11, -23<=k<=23, -14<=l<=14	
Reflections collected	7575	
Independent reflections	3947 [R(int) = 0.0262]	
Completeness to theta = 27.49°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3947 / 0 / 312	

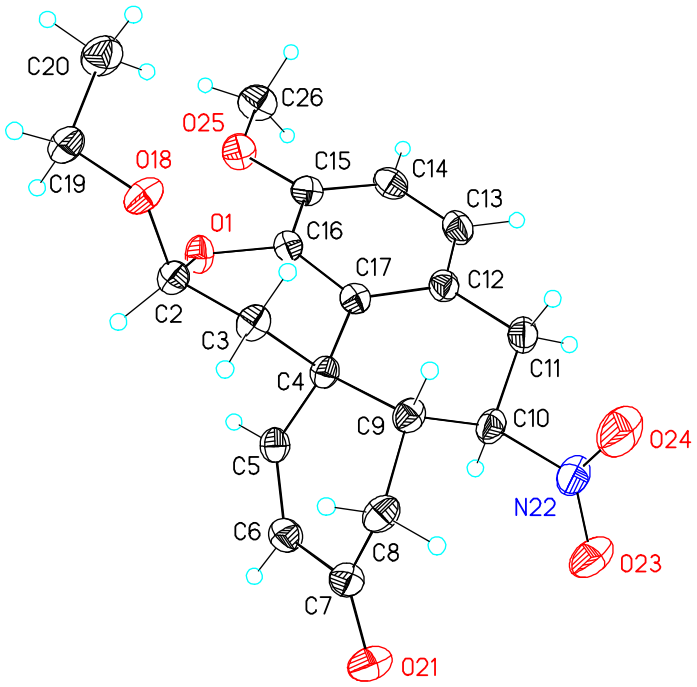
Goodness-of-fit on F^2	0.997
Final R indices	[I>2sigma(I)] R1 = 0.0445, wR2 = 0.1018
R indices (all data)	R1 = 0.0737, wR2 = 0.1162
Extinction coefficient	$6.1(11)x10^{-6}$
Largest diff. peak and hole	0.269 and -0.241 e.$Å^{-3}$

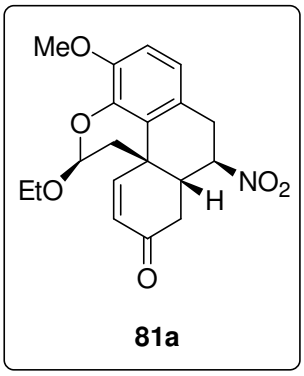
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for nitroalkene **80b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	8043(1)	4850(1)	4287(1)	32(1)
C2	8033(2)	5636(1)	4065(1)	26(1)
C3	6858(2)	6029(1)	4761(1)	26(1)
C4	7076(2)	5852(1)	6108(1)	24(1)
C5	8725(2)	6055(1)	6663(1)	27(1)
C6	9062(2)	6565(1)	7494(2)	34(1)
C7	7825(2)	7044(1)	7874(2)	39(1)
C8	6309(2)	7044(1)	7049(2)	34(1)
C9	5769(2)	6254(1)	6753(1)	26(1)
C10	5382(2)	5842(1)	7852(1)	28(1)
C11	5758(2)	5146(1)	8103(2)	29(1)
C12	6535(2)	4695(1)	7269(1)	26(1)
C13	6658(2)	3941(1)	7421(2)	29(1)
C14	7222(2)	3509(1)	6534(1)	27(1)
C15	7653(2)	3823(1)	5489(1)	24(1)
C16	7557(2)	4591(1)	5339(1)	23(1)
C17	7015(2)	5024(1)	6226(1)	23(1)
O18	7613(1)	5737(1)	2853(1)	31(1)
C19	8787(2)	5518(1)	2081(2)	42(1)
C20	8453(4)	5877(2)	895(2)	73(1)
O21	8019(2)	7422(1)	8774(2)	67(1)
N22	4285(2)	6191(1)	8602(1)	37(1)
O23	3398(2)	6669(1)	8140(1)	42(1)
O24	4234(2)	5991(1)	9645(1)	64(1)
O25	8180(1)	3456(1)	4550(1)	29(1)
C26	8225(3)	2673(1)	4613(2)	36(1)

Appendix C: X-ray Data for the nitroalkane 81a.

Figure 1. View of nitroalkane **81a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





81a

X-ray Experimental for nitroalkane 81a

Crystals grew as pale yellow plates by slow evaporation from ether. The data crystal was a plate that had approximate dimensions; 0.27 x 0.14 x 0.03 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 235 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 218 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0396*P)^2 + (0.2873*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.102, with R(F) equal to 0.0386 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (1.8(3)x10^{-5})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroalkane **81a**.

Empirical formula	C19 H21 N O6	
Formula weight	359.37	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.7189(2) Å	α= 106.745(1)°.
	b = 9.8011(3) Å	β= 92.890(1)°.
	c = 11.0087(3) Å	γ = 109.487(1)°.
Volume	837.99(4) $Å^3$	
Z	2	
Density (calculated)	1.424 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	380	
Crystal size	0.27 x 0.14 x 0.03 mm	
Theta range for data collection	1.96 to 27.49°.	
Index ranges	-11<=h<=11, -12<=k<=10, -14<=l<=14	
Reflections collected	6291	
Independent reflections	3820 [R(int) = 0.0185]	
Completeness to theta = 27.49°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3820 / 0 / 320	

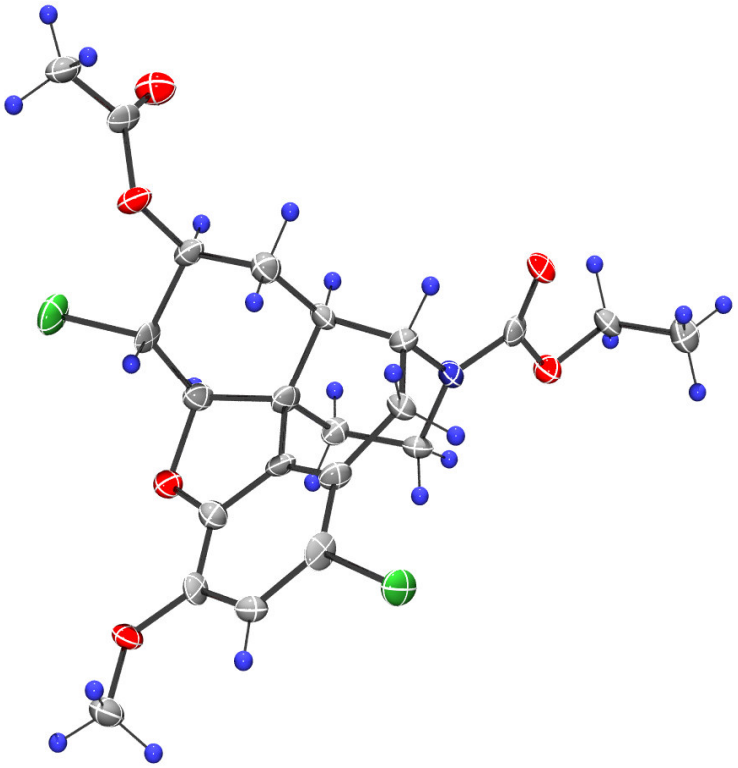
Goodness-of-fit on F^2	1.011
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0903
R indices (all data)	R1 = 0.0578, wR2 = 0.1020
Extinction coefficient	$1.8(3)x10^{-5}$
Largest diff. peak and hole	0.262 and -0.200 e.$Å^{-3}$

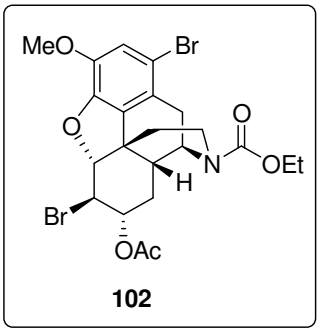
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nitroalkane **81a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	787(1)	1248(1)	4421(1)	24(1)
C2	-144(2)	2246(2)	4685(1)	22(1)
C3	781(2)	3804(2)	5687(1)	23(1)
C4	2114(2)	3776(1)	6644(1)	20(1)
C5	1307(2)	2661(2)	7343(1)	23(1)
C6	1120(2)	3062(2)	8573(1)	27(1)
C7	1634(2)	4666(2)	9381(1)	27(1)
C8	2025(2)	5800(2)	8655(1)	26(1)
C9	3044(2)	5405(2)	7603(1)	22(1)
C10	4742(2)	5520(2)	8181(1)	24(1)
C11	5836(2)	5292(2)	7172(1)	27(1)
C12	4971(2)	3795(2)	6111(1)	23(1)
C13	5860(2)	3043(2)	5362(1)	27(1)
C14	5084(2)	1690(2)	4345(1)	27(1)
C15	3383(2)	1098(2)	4023(1)	23(1)
C16	2475(2)	1873(2)	4750(1)	20(1)
C17	3244(2)	3163(2)	5826(1)	20(1)
018	-582(1)	2535(1)	3574(1)	28(1)
C19	-1540(2)	1203(2)	2495(1)	28(1)
C20	-518(2)	941(2)	1454(2)	36(1)
O21	1727(1)	5044(1)	10552(1)	36(1)
N22	5553(2)	7096(1)	9166(1)	29(1)
O23	5690(2)	7205(1)	10303(1)	38(1)
O24	5985(2)	8198(1)	8782(1)	51(1)
O25	2487(1)	-222(1)	3051(1)	29(1)
C26	3391(2)	-1065(2)	2328(2)	33(1)

Appendix D: X-ray data for the acetoxybromide 102.

Figure 1. View of acetoxybromide **102**. Displacement ellipsoids are scaled to the 50% probability level.





102

X-ray Experimental for the acetoxybromide 102

Crystals grew as colorless prisms by slow evaporation from hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.27 x 0.08 x 0.08 mm. The data were collected on a Rigaku R-Axis Spider diffractometer with an image plate detector using a graphite monochromator with CuKα radiation (λ = 1.5418Å). A total of 108 images of data were collected using ω-scans with a scan range of 5° and a counting time of 300 seconds per image. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0186*P)^2 + (6.627*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.172, with R(F) equal to 0.0702 and a goodness of fit, S, = 1.93. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1. Crystal data and structure refinement for the acetoxybromide **102**.

Empirical formula	C25 H32 Br2 N O6	
Formula weight	602.34	
Temperature	100(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 15.8880(10) Å	α= 90°.
	b = 7.2820(3) Å	β= 90.706(2)°.
	c = 21.5351(13) Å	γ = 90°.
Volume	2491.3(2) $Å^3$	
Z	4	
Density (calculated)	1.606 Mg/m^3	
Absorption coefficient	4.474 mm^{-1}	
F(000)	1228	
Crystal size	0.3 x 0.2 x 0.1 mm	
Theta range for data collection	6.69 to 67.48°.	
Index ranges	-17<=h<=10, -8<=k<=8, -25<=l<=25	
Reflections collected	20964	
Independent reflections	3910 [R(int) = 0.0570]	
Completeness to theta = 67.48°	87.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.64 and 0.35	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3910 / 0 / 283
Goodness-of-fit on F^2	1.928
Final R indices [I>2sigma(I)]	R1 = 0.0741, wR2 = 0.1622
R indices (all data)	R1 = 0.0834, wR2 = 0.1702
Largest diff. peak and hole	1.193 and -1.049 e.$Å^{-3}$

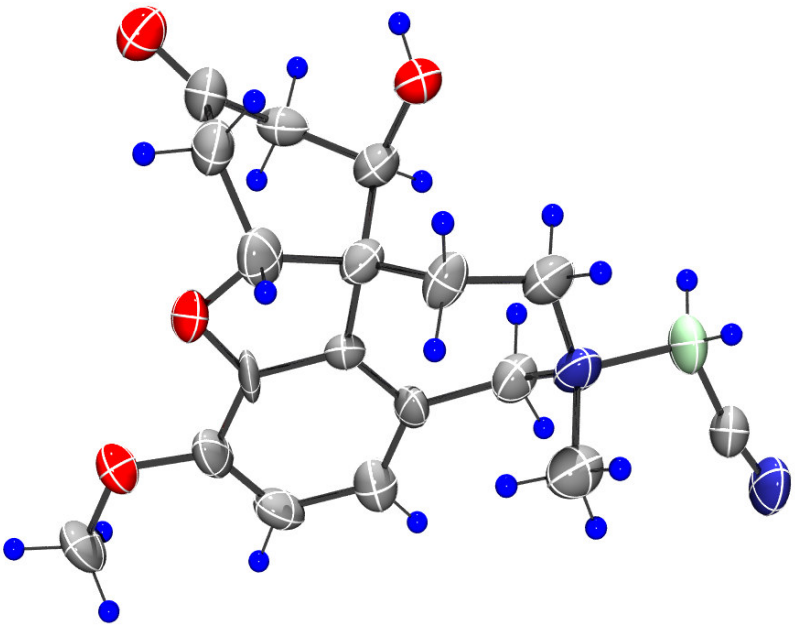
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for acetoxybromide **102**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

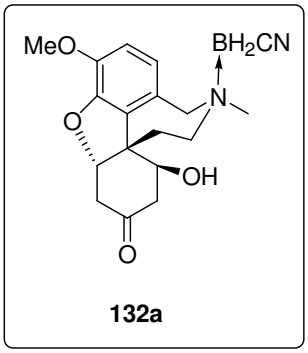
	x	y	z	U(eq)
Br1	-409(1)	2769(1)	4004(1)	32(1)
Br2	4777(1)	-1213(1)	3949(1)	39(1)
O1	2731(3)	-1984(6)	4365(2)	27(1)
C2	3318(5)	-601(9)	4673(3)	26(2)
C3	2707(5)	730(10)	5015(3)	26(2)
C4	2525(5)	-21(9)	5673(3)	23(2)
C5	1821(5)	1113(9)	5962(3)	26(2)
N6	2001(4)	3085(7)	5927(3)	26(1)
C7	2202(5)	3802(9)	5296(3)	25(2)
C8	1397(5)	3677(9)	4838(3)	26(2)
C9	1281(5)	1835(9)	4515(3)	24(2)
C10	597(5)	1276(9)	4112(3)	29(2)
C11	584(5)	-409(9)	3786(3)	24(2)
C12	1283(5)	-1596(9)	3840(3)	26(2)
C13	1960(5)	-1047(9)	4246(3)	26(2)
C14	3795(4)	319(9)	4150(3)	24(2)
C15	4106(5)	2256(10)	4314(3)	25(2)
C16	3353(5)	3477(10)	4468(3)	28(2)
C17	2982(5)	2760(9)	5083(3)	23(2)
C18	1929(5)	569(9)	4580(3)	24(2)
C19	2088(5)	4243(9)	6434(3)	23(2)
O20	2266(3)	5840(6)	6407(2)	28(1)
O21	1891(3)	3356(6)	6976(2)	27(1)
C22	2074(5)	4437(9)	7554(3)	28(2)
C23	1344(5)	5702(10)	7686(3)	33(2)

O24	1348(3)	-3231(6)	3529(2)	26(1)
C25	661(5)	-3684(10)	3081(4)	35(2)
O26	4493(3)	2989(7)	3761(2)	29(1)
C27	5281(5)	3760(9)	3859(4)	27(2)
O28	5670(4)	3879(7)	4365(2)	39(1)
C29	5600(5)	4452(10)	3242(3)	35(2)

Appendix E: X-ray data for the β-hydroxyketone 132a.

Figure 1. View of β-hydroxyketone **132a**. Displacement ellipsoids are scaled to the 50% probability level.





132a

X-ray Experimental for β-hydroxyketone 132a

Crystals grew as colorless laths by slow evaporation from methanol. The data crystal was cut from a larger crystal and had approximate dimensions; 0.12 x 0.02 x 0.02 mm. The data were collected on a Rigaku R-Axis Spider diffractometer with an image plate detector using a graphite monochromator with CuKα radiation (λ = 1.5418Å). A total of 144 images of data were collected using ω-scans with a scan range of 5° and a counting time of 450 seconds per image. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.03*P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.214, with R(F) equal to 0.148 and a goodness of fit, S, = 1.75. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1. Crystal data and structure refinement for β-hydroxyketone **132a**.

Identification code	shelxl	
Empirical formula	C18 H23 B N2 O4	
Formula weight	342.19	
Temperature	100(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 27.2222(4) Å	α= 90°.
	b = 6.6121(1) Å	β= 105.697(1)°.
	c = 19.9706(5) Å	γ = 90°.
Volume	3460.57(11) $Å^3$	
Z	8	
Density (calculated)	1.314 Mg/m^3	
Absorption coefficient	0.748 mm^{-1}	
F(000)	1456	
Crystal size	0.12 x 0.02 x 0.02 mm^3	
Theta range for data collection	6.91 to 67.49°.	
Index ranges	-32<=h<=28, -7<=k<=7, -23<=l<=23	
Reflections collected	29423	
Independent reflections	6137 [R(int) = 0.1265]	
Completeness to theta = 67.49°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.82	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6137 / 0 / 458
Goodness-of-fit on F^2	1.753
Final R indices [I>2sigma(I)]	R1 = 0.1482, wR2 = 0.1543
R indices (all data)	R1 = 0.2992, wR2 = 0.2138
Extinction coefficient	0.00167(17)
Largest diff. peak and hole	0.601 and -0.565 e.$Å^{-3}$

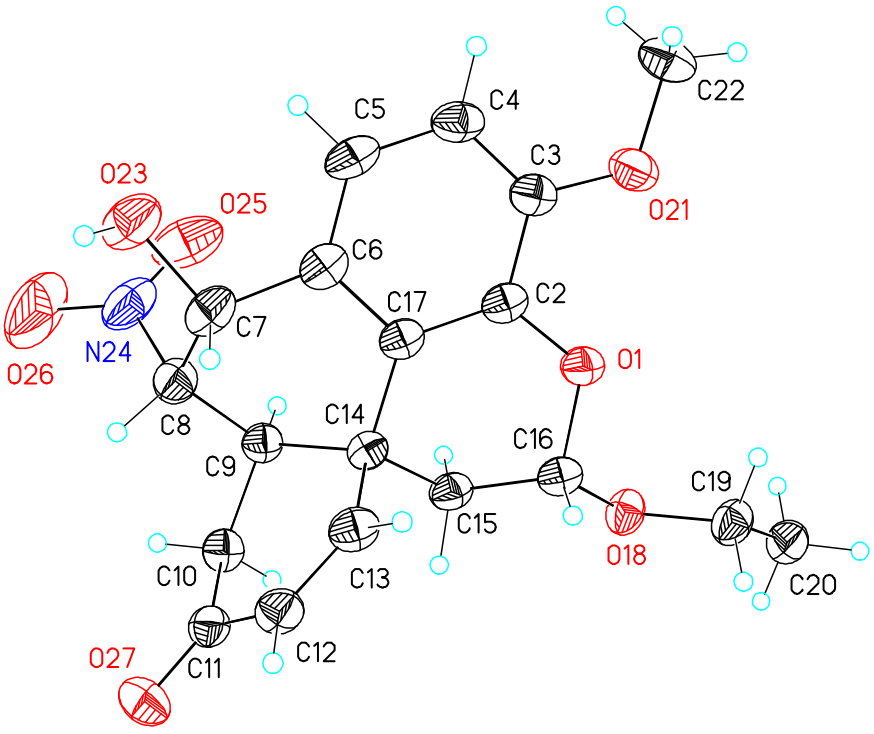
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for β-hydroxyketone **102a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

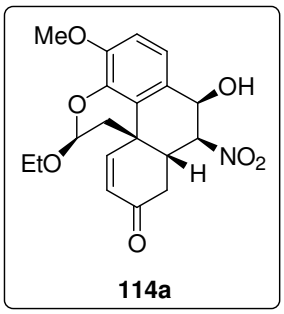
	x	y	z	U(eq)
O1A	8589(2)	5565(7)	4376(2)	49(2)
O2A	8455(2)	3280(7)	2618(3)	58(2)
O3A	9232(2)	-220(8)	4089(2)	51(2)
O4A	7812(2)	7433(8)	4778(2)	51(2)
N1A	9027(2)	-3448(9)	7684(3)	55(2)
B1A	9381(3)	-2540(13)	6577(5)	54(3)
C1A	9054(3)	4366(12)	4418(4)	51(2)
C2A	9079(3)	4165(11)	3673(4)	54(2)
C3A	8629(3)	2976(12)	3233(5)	52(3)
C4A	8421(3)	1429(10)	3629(4)	45(2)
C5A	8802(3)	665(12)	4288(4)	53(2)
C6A	9009(3)	2378(12)	4805(4)	41(2)
C7A	9519(3)	1898(10)	5312(3)	43(2)
C8A	9531(3)	-108(11)	5698(3)	54(2)
N9A	9250(2)	-268(9)	6265(3)	46(2)
C10A	8676(3)	-30(11)	5988(3)	46(2)
C11A	8475(3)	2013(11)	5706(4)	38(2)
C12A	8101(3)	2953(12)	5945(4)	47(2)
C13A	7863(3)	4777(12)	5656(4)	49(2)
C14A	8005(3)	5699(13)	5102(4)	48(2)
C15A	8393(3)	4755(11)	4887(4)	37(2)
C16A	8607(3)	2971(11)	5160(4)	32(2)
C17A	9149(3)	-2944(12)	7211(4)	46(2)
C18A	9455(2)	1277(10)	6816(3)	58(2)
C19A	7419(3)	8416(10)	5008(3)	61(2)
O1	6476(2)	-551(7)	5618(3)	46(2)
O2	6513(2)	1156(7)	3801(3)	55(2)

O3	5768(2)	4928(7)	4619(2)	48(2)
O4	7278(2)	-2039(8)	6673(2)	52(2)
N1	5924(2)	8768(9)	8345(3)	56(2)
B1	5574(3)	7767(13)	6966(4)	58(3)
C1	5996(3)	457(11)	5263(4)	45(2)
C2	5942(3)	387(11)	4488(4)	51(2)
C3	6364(3)	1584(13)	4305(4)	55(3)
C4	6588(3)	3288(11)	4781(3)	45(2)
C5	6205(3)	4186(11)	5139(4)	48(2)
C6	6034(3)	2597(11)	5592(4)	35(2)
C7	5510(3)	3137(10)	5704(3)	43(2)
C8	5468(2)	5180(11)	6021(3)	46(2)
N9	5738(2)	5517(9)	6780(3)	44(2)
C10	6323(3)	5477(11)	6925(3)	52(2)
C11	6559(3)	3428(12)	6864(4)	41(2)
C12	6947(3)	2719(12)	7426(4)	44(2)
C13	7191(3)	896(12)	7379(4)	51(2)
C14	7064(3)	-192(13)	6778(5)	48(2)
C15	6661(3)	469(15)	6224(4)	50(3)
C16	6431(3)	2309(12)	6274(4)	41(2)
C17	5797(3)	8274(11)	7771(5)	48(2)
C18	5586(2)	3984(10)	7236(3)	53(2)
C19	7679(3)	-2751(10)	7259(4)	58(2)

Appendix F: X-ray data for the nitroalcohol 114a.

Figure 1. View of nitroalcohol **114a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





114a

X-ray Experimental for nitroalcohol 114a:

Crystals grew as colorless prisms by slow evaporation from toluene. The data crystal was cut from a larger crystal and had approximate dimensions; 0.22 x 0.22 x 0.12 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 184 frames of data were collected using ω-scans with a scan range of 1.8° and a counting time of 66 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0596*P)^2 + (1.1616*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.161, with R(F) equal to 0.0653 and a goodness of fit, S, = 1.04. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroalcohol **114a**.

Empirical formula	C19 H21 N O7	
Formula weight	375.37	
Temperature	153(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 11.3843(6) Å	α= 90°.
	b = 17.2041(11) Å	β= 102.762(2)°.
	c = 9.1689(8) Å	γ = 90°.
Volume	1751.4(2) $Å^3$	
Z	4	
Density (calculated)	1.424 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	792	
Crystal size	0.22 x 0.22 x 0.12 mm	
Theta range for data collection	1.83 to 27.47°.	
Index ranges	-14<=h<=14, -22<=k<=17, -11<=l<=11	
Reflections collected	6616	
Independent reflections	3990 [R(int) = 0.0339]	
Completeness to theta = 27.47°	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3990 / 0 / 247	
Goodness-of-fit on F^2	1.036	

Final R indices [I>2sigma(I)]	R1 = 0.0653, wR2 = 0.1354
R indices (all data)	R1 = 0.1283, wR2 = 0.1606
Largest diff. peak and hole	0.594 and -0.296 e.Å^{-3}

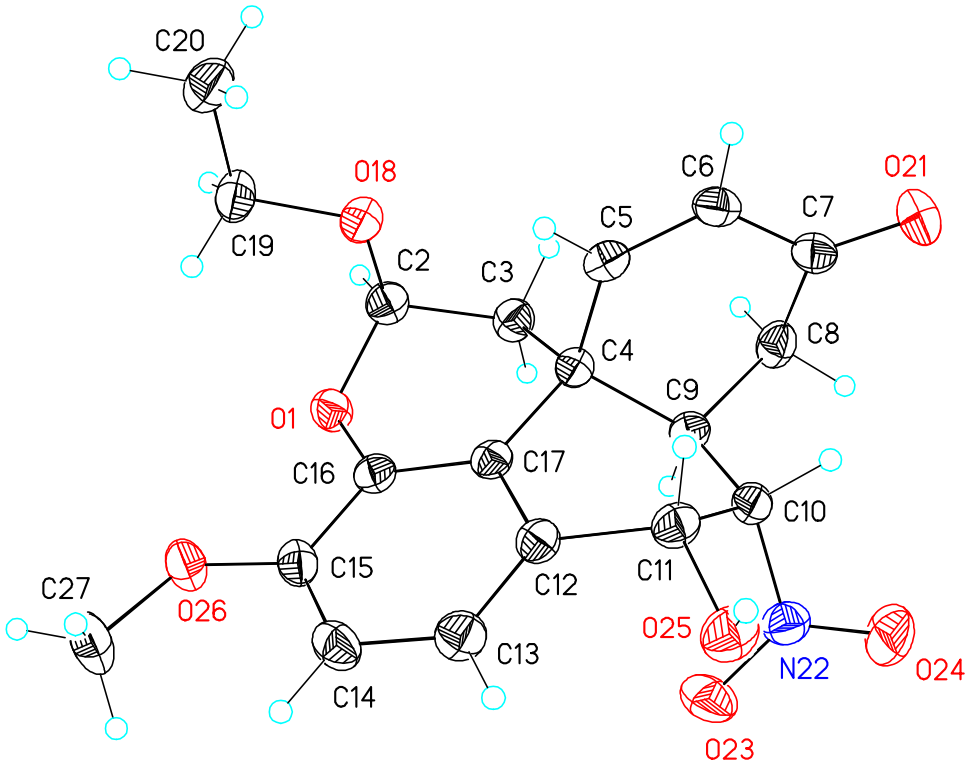
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nitroalcohol **114a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

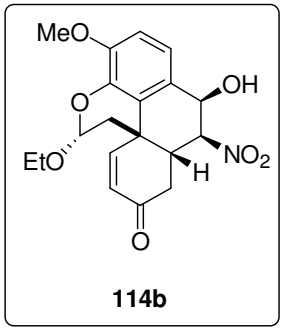
	x	y	z	U(eq)
O1	5348(2)	1216(1)	3823(2)	32(1)
C2	4795(2)	1392(1)	4970(3)	27(1)
C3	5519(2)	1776(1)	6201(3)	30(1)
C4	5041(3)	1954(2)	7422(3)	34(1)
C5	3860(3)	1758(2)	7431(3)	35(1)
C6	3137(2)	1400(1)	6207(3)	29(1)
C7	1862(2)	1168(2)	6166(3)	36(1)
C8	1013(2)	1376(2)	4664(3)	35(1)
C9	1548(2)	1326(1)	3260(3)	27(1)
C10	645(2)	945(1)	1968(3)	30(1)
C11	471(2)	93(2)	2228(3)	30(1)
C12	1481(2)	-324(1)	3168(3)	33(1)
C13	2519(2)	21(2)	3776(3)	32(1)
C14	2766(2)	879(1)	3572(3)	27(1)
C15	3377(2)	986(2)	2238(3)	30(1)
C16	4673(2)	737(2)	2631(3)	30(1)
C17	3601(2)	1219(1)	4951(3)	27(1)
O18	5180(2)	849(1)	1409(2)	32(1)
C19	6340(2)	484(2)	1538(3)	35(1)
C20	6856(2)	771(2)	272(3)	39(1)
O21	6660(2)	1947(1)	6059(2)	38(1)
C22	7432(3)	2320(2)	7307(3)	43(1)
O23	1445(2)	1530(1)	7361(2)	50(1)
N24	620(3)	2210(2)	4854(3)	51(1)
O25	1389(2)	2718(1)	5005(2)	61(1)

O26	-436(2)	2304(2)	4893(3)	97(1)
O27	-469(2)	-233(1)	1642(2)	41(1)

Appendix G: X-ray data for the nitroalcohol 114b.

Figure 1. View of nitroalcohol **114b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





114b

X-ray Experimental for the nitroalcohol 114b

Crystals grew as colorless prisms by slow evaporation from toluene. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.21 x 0.12 x 0.11 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 146 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 138 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.1 The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atom bound to O25 was observed in a ΔF map and refined with an isotropic displacement parameter. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(Fo))^2 + (0.0486*P)^2 + (0.4664*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.129, with R(F) equal to 0.0558 and a goodness of fit, S = 1.02. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroalcohol **114b**.

Empirical formula	C19 H21 N O7	
Formula weight	375.37	
Temperature	153(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 14.7812(8) Å	α= 90°.
	b = 7.9289(6) Å	β= 116.551(4)°.
	c = 16.4024(12) Å	γ = 90°.
Volume	1719.6(2) $Å^3$	
Z	4	
Density (calculated)	1.450 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	792	
Crystal size	0.20 x 0.12 x 0.11 mm	
Theta range for data collection	2.92 to 27.37°.	
Index ranges	-19<=h<=19, -10<=k<=9, -21<=l<=21	
Reflections collected	6592	
Independent reflections	3884 [R(int) = 0.0601]	
Completeness to theta = 27.37°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3884 / 0 / 250	

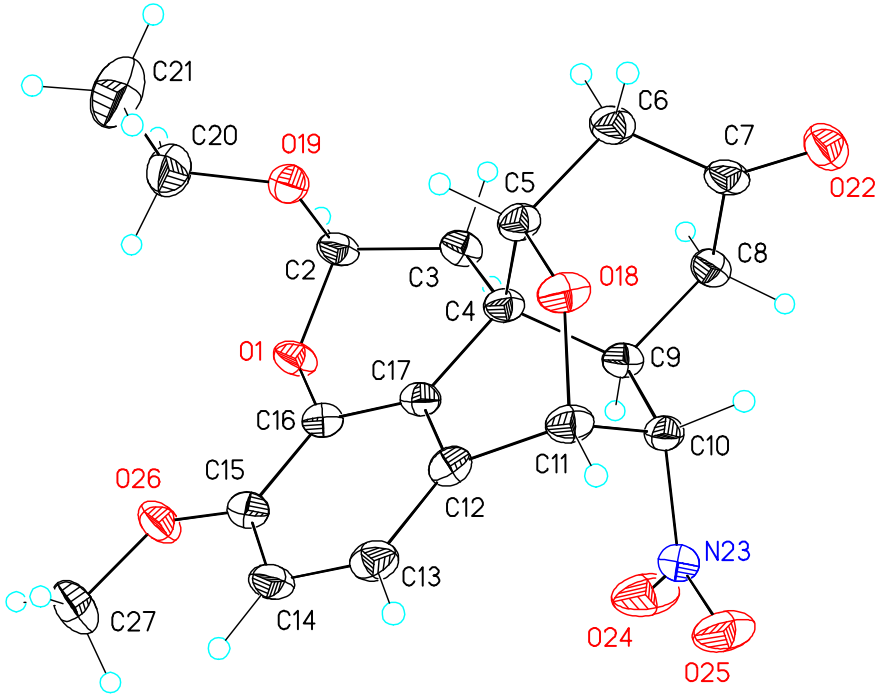
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0558, wR2 = 0.1090
R indices (all data)	R1 = 0.1151, wR2 = 0.1286
Largest diff. peak and hole	0.264 and -0.269 e.$Å^{-3}$

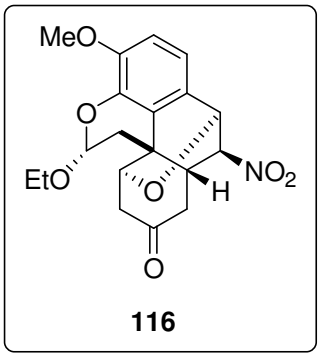
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for nitroalcohol **114b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	5535(1)	1950(2)	2876(1)	26(1)
C2	5461(2)	2397(3)	3691(2)	26(1)
C3	4626(2)	3669(3)	3476(2)	25(1)
C4	4810(2)	5338(3)	3077(1)	21(1)
C5	5475(2)	6470(3)	3860(1)	24(1)
C6	5126(2)	7702(3)	4198(2)	26(1)
C7	4039(2)	8128(3)	3809(2)	27(1)
C8	3335(2)	6895(3)	3123(2)	27(1)
C9	3793(2)	6261(3)	2507(1)	22(1)
C10	3923(2)	7780(3)	1972(1)	23(1)
C11	4929(2)	7898(3)	1920(2)	25(1)
C12	5329(2)	6174(3)	1861(2)	23(1)
C13	5732(2)	5819(3)	1264(2)	29(1)
C14	6092(2)	4215(3)	1230(2)	29(1)
C15	6036(2)	2969(3)	1787(2)	24(1)
C16	5619(2)	3303(3)	2388(1)	22(1)
C17	5282(1)	4920(3)	2442(1)	20(1)
O18	6374(1)	3051(2)	4341(1)	27(1)
C19	7190(2)	1847(3)	4593(2)	32(1)
C20	8109(2)	2506(3)	5396(2)	36(1)
O21	3736(1)	9410(2)	4015(1)	38(1)
N22	3066(1)	7700(2)	1018(1)	29(1)
O23	3119(1)	6701(2)	476(1)	38(1)
O24	2344(1)	8630(2)	848(1)	54(1)
O25	4806(1)	8966(2)	1187(1)	34(1)
O26	6356(1)	1322(2)	1807(1)	31(1)
C27	6942(2)	974(3)	1327(2)	43(1)

Appendix H: X-ray data for the nitroether 116.

Figure 1. View of nitroether **116** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





116

X-ray Experimental for nitroether 116.

Crystals grew as colorless plates by slow evaporation from chloroform. The data crystal was cut from a larger crystal and had approximate dimensions; 0.33 x 0.30 x 0.05 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 99 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 154 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0608*P)^2 + (13.1411*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.152, with R(F) equal to 0.0567 and a goodness of fit, S, = 0.990. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for nitroether **116**.

Empirical formula	$C_{20.50}H_{22.50}Cl_{4.50}NO_7$	
Formula weight	554.42	
Temperature	153(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 27.5026(15) Å	α= 90°.
	b = 12.6167(8) Å	β= 114.238(2)°.
	c = 15.2499(12) Å	γ = 90°.
Volume	4825.1(6) $Å^3$	
Z	8	
Density (calculated)	1.526 Mg/m^3	
Absorption coefficient	0.588 mm^{-1}	
F(000)	2280	
Crystal size	0.33 x 0.30 x 0.05 mm	
Theta range for data collection	2.11 to 27.47°.	
Index ranges	-35<=h<=35, -16<=k<=14, -19<=l<=19	
Reflections collected	9042	
Independent reflections	5429 [R(int) = 0.0318]	
Completeness to theta = 27.47°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.82	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	5429 / 30 / 318
Goodness-of-fit on F^2	0.982
Final R indices [I>2sigma(I)]	R1 = 0.0567, wR2 = 0.1312
R indices (all data)	R1 = 0.0937, wR2 = 0.1525
Largest diff. peak and hole	0.774 and -0.626 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nitroether **116**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl1A	866(1)	7546(1)	3052(1)	67(1)
Cl2A	387(1)	7039(1)	4348(1)	74(1)
Cl3A	487(1)	9222(1)	3888(1)	105(1)
C1A	781(1)	7975(3)	4070(3)	52(1)
Cl1B	-372(1)	4687(2)	3594(2)	85(1)
Cl2B	-527(3)	4193(5)	1673(3)	65(1)
Cl3B	537(2)	4415(6)	3118(5)	107(2)
C1B	-117(3)	4855(5)	2727(5)	51(2)
O1	3218(1)	2656(1)	5882(1)	25(1)
C2	3120(1)	3049(2)	6684(2)	23(1)
C3	2612(1)	3701(2)	6346(2)	22(1)
C4	2617(1)	4646(2)	5713(2)	20(1)
C5	2850(1)	5687(2)	6271(2)	21(1)
C6	2522(1)	6125(2)	6792(2)	25(1)
C7	1943(1)	6249(2)	6124(2)	23(1)
C8	1696(1)	5305(2)	5486(2)	23(1)
C9	2045(1)	4930(2)	4968(2)	21(1)
C10	2087(1)	5809(2)	4300(2)	21(1)
C11	2674(1)	6136(2)	4614(2)	22(1)
C12	2992(1)	5190(2)	4582(2)	21(1)
C13	3300(1)	5054(2)	4066(2)	25(1)
C14	3567(1)	4099(2)	4139(2)	26(1)
C15	3539(1)	3296(2)	4742(2)	24(1)
C16	3229(1)	3451(2)	5271(2)	21(1)
C17	2955(1)	4382(2)	5176(2)	20(1)

O18	2841(1)	6506(1)	5589(1)	24(1)
O19	3545(1)	3685(1)	7275(1)	25(1)
C20	4042(1)	3117(3)	7710(2)	38(1)
C21	4460(1)	3872(3)	8328(3)	60(1)
O22	1696(1)	7057(1)	6085(1)	29(1)
N23	1876(1)	5479(2)	3251(2)	24(1)
O24	1754(1)	4566(2)	3015(2)	44(1)
O25	1861(1)	6178(2)	2684(1)	37(1)
O26	3789(1)	2334(2)	4877(1)	30(1)
C27	4140(1)	2178(3)	4409(2)	40(1)

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4) $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection.

   $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$.

   $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

5) Tables 4.2.6.8 and 6.1.1.4 in *International Tables for X-ray Crystallography Vol. C*; Wilson, A. J. C., Ed.; Kluwer Academic Press: Boston, **1992**.

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List of Abbreviations

Å	ångström unit
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BHT	butylated hydroxytoluene
Bn	benzyl
bs	broad singlet
Bu	butyl
c	concentration
cat.	catalytic
CI	chemical ionization
Cy	cyclohexyl
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
D	Sodium D-line; 589 nanometers
DBH	3,5-dibromo-5,5-dimethylhydantoin
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double of doublets

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
Dioxane	1,4-dioxane
DME	1,4-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dt	doublet of triplets
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
g	gram
h	hour
[H]	reduction
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
imid.	imidazole
IR	infrared
LAH	lithium aluminum hydride
m	multiplet
m	meta
M	molar
Me	methyl
mM	millimole
min	minute

MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MsOH	methanesulfonic acid
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
o	ortho
[O]	oxidation
ORTEP	Oak Ridge thermal ellipsoid program
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
Pr	propyl
prep	preparative
pyr.	pyridine
R	generic functional group
q	quartet
qd	quadruplet of doublets
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride

TBDPS	*tert*-butyldiphenylsilyl
TBDS or TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
Td	triplet of doublets
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	toluenesulfonyl
TsOH or *p*TSA	toluenesulfonic acid
X	halogen

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